Universidade de Lisboa

Faculdade de Farmácia

PARENTAL RISK PERCEPTION OF VACCINE'S ADVERSE REACTIONS IN PAEDIATRIC POPULATION AND ITS IMPACT ON VACCINE COMPLIANCE: THE CASE OF PORTUGAL SINCE 2012

Marta Soraia Sousa Fernandes

Dissertação orientada pela Professora Doutora Ana Paula Martins e, coorientada pela Mestre Paula Barão

Regulação e Avaliação do Medicamento e Produtos de Saúde

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ABSTRACT

Background: The implementation of routine and mass vaccination programmes allowed the control of once life-threatening diseases like diphtheria and tetanus. Immunisation benefits were so satisfying that today we are facing the consequences of its own success. As parents have become less familiar with these diseases, they have become more concerned about the safety and necessity of vaccines.

This study aims to analyse adverse events following immunisation in the Portuguese paediatric population (2012 – 2016), explore vaccine trends in Portugal and compare the records from Portugal and The Netherlands. Additionally, the factors and reasons for vaccine hesitancy in high-income countries are addressed through a systematic review.

Methods: We conducted a retrospective study on adverse drug reactions in paediatrics to DTPa and MMR vaccine in Portugal, from 2012 to 2016. Public information on vaccine coverage and vaccine preventable disease cases in Portugal and in The Netherlands, was explored and compared. We conducted a systematic review on the factors behind vaccine hesitancy among parents in high-income countries.

Results: From 2012 to 2016 a total of 591 ADR reports, concerning Portuguese paediatric individuals exposed to DTPa, and/ or to MMR vaccines, were analysed. The system organ class most frequently involved in ADR reports was general disorders and administration site conditions. In Portugal, the national immunization program participation ranges from 96,1% to 99,1% vaccine coverage. In this study, it is possible to observe vaccination coverage decline over the selected cohorts in the Netherlands. Vaccine safety was the most recorded factor of vaccine hesitancy in the systematic review.

Conclusions: Adverse drug reaction reporting to vaccines in the Portuguese paediatric population is slightly decreasing over the years. Vaccination coverage in Portugal is very high. In The Netherlands vaccination coverage is decreasing. In Portugal, vaccine preventable disease cases in the paediatric population is consistently lower than in The Netherland. Parental risk perception of adverse drug reactions to vaccines is playing an important role on parental compliance with the national immunization program in high-income countries, which may lead to vaccine hesitancy or vaccine refusal.

Keywords: Immunization, Adverse Drug Following Immunization, Vaccine Coverage, Vaccine Preventable Diseases, Vaccine Hesitancy

RESUMO

Introdução: A imunização é considerada a medida de saúde pública mais bem-sucedida e com melhor eficácia, logo após a água potável. A implementação dos programas de vacinação em massa permitiu a erradicação da varíola, a eliminação da poliomielite em diversas regiões do globo e o controlo de muitas doenças contagiosas, anteriormente mortais, tais como a difteria e o tétano.

Qualquer substância capaz de produzir um efeito terapêutico, não se encontra isenta de produzir efeitos não desejados ou efeitos adversos, nenhum medicamento que seja farmacologicamente eficaz é completamente desprovido de riscos. A reação adversa a medicamentos é uma significante causa de mortalidade e morbilidade, especialmente na população pediátrica, e é fortemente associada a um importante custo económico com a saúde. Todas as vacinas autorizadas no mercado Europeu são rigorosamente testadas e monitorizadas, com elevados padrões de segurança, eficácia e qualidade. Milhões de vacinas são administradas em crianças anualmente, as reações adversas graves são incomuns e as mortes causadas pela administração de vacinas são muito raras. O Sistema Nacional de Farmacovigilância é responsável pela deteção, registo e avaliação das reações adversas, com o objetivo de determinar a incidência, gravidade e causalidade com os medicamentos, baseadas no estudo sistemático e multidisciplinar dos efeitos dos medicamentos. A notificação espontânea é um instrumento muito importante na monitorização da farmacovigilância, o principal objetivo da notificação espontânea é sinalizar novas reações adversas, que não foram encontradas antes da comercialização do medicamento, o mais rapidamente possível. O Sistema Nacional de Farmacovigilância é coordenado pelo Grupo de Gestão de Risco do Medicamento do INFARMED, I.P., quando a notificação de uma reação adversa grave é recebida pelo INFARMED, toda a informação é avaliada por uma equipa especialista em segurança do medicamento, para verificar se a reação adversa pode ter ocorrido devido à administração da vacina. Em Portugal, os médicos, farmacêuticos, indústria e utentes estão autorizados a reportar reações adversas a medicamentos às unidades de farmacovigilância.

O Programa Nacional de Vacinação português está disponível para todos os cidadãos que se encontrem presentes em Portugal, incluindo imigrantes legais ou ilegais. Estão incluídas onze vacinas, que são recomendadas a todas as crianças com idades inferiores a 18 anos. O objetivo do calendário de vacinação recomendado é atingir a melhor proteção na idade mais adequada e o mais cedo possível, porque é no primeiro ano de idade que a criança é mais vulnerável a doenças infeciosas.

Apesar da cobertura vacinal em Portugal ser considerada elevada e os casos de doenças estarem controlados, as autoridades nacionais estão atentas a movimentos anti

vacinação que estão a emergir na Europa, de que é exemplo a Holanda. A Holanda possui grupos já identificados de pais que recusam a vacinação, incluindo protestantes que residem na região do Cinturão Bíblico. Os membros das Congregações Reformadas acreditam que a vacinação é contra os preceitos de Deus. Os Antroposóficos acreditam que experienciar algumas doenças infeciosas contribui para reforçar o corpo e a mente.

O Programa Nacional de Vacinação holandês inclui as mesmas vacinas que em Portugal. Apesar da cobertura vacinal na Holanda ser considerada elevada, tem-se vindo a observar nos últimos anos um declínio. Estas flutuações foram inicialmente observadas a nível regional, no entanto são agora comuns a toda a nação. Apesar de uma variedade de fatores desconhecidos poderem estar na origem deste declínio, a hesitação à vacinação por parte dos pais pode constituir um importante determinante neste campo.

As vacinas são geralmente administradas em sujeitos saudáveis, normalmente em populações vulneráveis, como é o caso das crianças, pelo que as reações adversas têm um grande impacto na aceitação da imunização assim como na avaliação do benefício-risco. As atitudes, experiências e contexto social dos pais são determinantes na decisão de vacinar ou não a criança. O conhecimento que os pais têm face às doenças que podem ser prevenidas por vacinas, influenciam a sua perceção relativamente à gravidade da doença e à probabilidade das suas crianças virem a ser infetadas. Indivíduos hesitantes à vacinação demonstram níveis de indecisão variáveis sobre vacinas específicas ou sobre a vacinação em geral. Podem aceitar todas as vacinas, mas permanecer preocupados quanto à sua administração, alguns pais podem recusar ou adiar algumas vacinas, mas aceitar outras, outros indivíduos podem recusar todas as vacinas. O comportamento dos indivíduos hesitantes à vacinação é complexo e os determinantes da hesitação vacinal são altamente variáveis ao longo do tempo, espaço e vacina.

Os benefícios da imunização foram tão satisfatórios que hoje enfrentamos as consequências do seu próprio sucesso. À medida que os pais foram ficando menos familiarizados com estas doenças, começaram a ficar mais atentos e preocupados quanto à segurança e necessidade das vacinas. Isto levanta uma grande preocupação quanto ao futuro do Programa Nacional de Vacinação, se a cobertura vacinal continuar a descer, não seremos capazes de manter a imunidade de grupo e consequentemente a população ficará suscetível às doenças prevenidas por vacinas.

Este estudo pretende analisar os casos de reações adversas a vacinas na população pediátrica portuguesa (2012 – 2016), explorar a tendência vacinal em Portugal e comparar os indicadores de cobertura vacinal de Portugal e da Holanda. Adicionalmente, através de uma revisão sistemática da literatura, serão investigados os fatores que explicam a hesitação em países industrializados.

Métodos: Foi realizada uma análise retrospetiva sobre das adversas (RAMS) às vacinas DTPa e VASPR ocorridas na população pediátrica, em Portugal, no período entre 2012 e 2016. Foi analisada a informação publicada sobre a cobertura vacinal e o número de casos de doenças prevenidas por vacinas em Portugal e na Holanda. Foi realizada uma revisão sistemática de literatura sobre os fatores etiológicos da hesitação à vacinação em países industrializados.

Resultados: Desde 2012 a 2016 um total de 591 notificações de reações adversas às vacinas DTPa e VASPR, na população pediátrica portuguesa, foram analisadas. A faixa etária com maior número de notificações foi entre os 3 anos (inclusive) e os 12 anos (exclusive). O código ATC mais frequentemente envolvido nas notificações de reação adversa foi o J07CA02 vacina contra a difteria, o tétano, a tosse convulsa e a poliomielite. A classe de sistema de órgãos mais prevalente nas notificações foi transtornos gerais e condições do local de administração. Em 55,33% as reações adversas foram consideradas graves, 71,06% dos indivíduos com a reação adversa recuperaram completamente. A maior percentagem de reações adversas foi reportada pelo enfermeiro.

Em Portugal, a cobertura vacinal do programa nacional de vacinação varia entre 96,1% e 99,1%, o que de acordo com este estudo, contrasta com os valores de cobertura vacinal apresentados pela Holanda, que variam desde 19.7% a 96.1%. Este estudo evidencia também, um declínio na cobertura vacinal das coortes selecionadas na Holanda que se tem vindo a repetir durante os últimos anos.

Foram diversos os fatores identificados como estando associados à hesitação à vacinação. Foram identificados como fatores respetivamente, as características específicas dos pais, fatores relacionados com as vacinas e fatores relacionados com a doença. O fator mais referido na revisão sistemática de literatura foi a segurança vacinal.

Conclusão: A notificação de reações adversas a vacinas na população pediátrica portuguesa está a diminuir ao longo dos anos. A cobertura vacinal em Portugal é elevada. Na Holanda, a cobertura vacinal está a diminuir. Em Portugal, o número de casos de doenças prevenidas por vacinas é substancialmente inferior aos dados registados na Holanda. A perceção de risco dos pais face às reações adversas a vacinas constitui um importante fator no cumprimento do plano nacional de vacinação nos países industrializados, o que pode gerar hesitação à vacinação ou mesmo a recusa vacinal.

Palavras-chave: Imunização, Reação Adversa, Cobertura Vacinal, Doenças Prevenidas por Vacinas, Hesitação à Vacinação

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LIST OF ABBREVIATIONS

ADR – Adverse Drug Reaction

AEFI – Adverse Event Following Immunization

ATC – Anatomical Therapeutic Chemical

BCG – Bacillus Calmette-Guérin

DGS – Directorate General Health

DNA – Deoxyribonucleic Acid

DTPa – Diphtheria, Tetanus and acellular Pertussis Vaccine

DTP – Diphtheria, Tetanus, and Pertussis

ECDC – European Centre for Disease Prevention and Control

EMA – European Medicines Agency

EU/ EEA – European Union/ European Economic Area

FDA – Food and Drug Administration

HBV – Hepatitis B Vaccine

Hib – Haemophilus influenzae type b

INFARMED I. P. – National Authority for Medicines and Health Products, I.P.

IPV – Inactivated Polio Vaccines

MedDRA – Medical Dictionary for Regulatory Activities

MedDRA PT – Medical Dictionary for Regulatory Activities Preferred Term

MenC – Meningococcal C

MMR – Measles, Mumps, Rubella

MPL – Monophosphoryl Lipid A

NIP – National Immunization Program

NPS – National Pharmacovigilance System

PL – Package Leaflet

Pn13 – Pneumococcal 13-valent Vaccine

PRAC – Pharmacovigilance Risk Assessment Committee

RPU – Regional Pharmacovigilance Unit

SAGE – Strategic Advisory Group of Experts on Immunization

SmPC – Summary of Product Characteristics

SOC – System Organ Class

Td – Tetanus and Diphtheria

VPD – Vaccine Preventable Disease

WHO – World Health Organization

1. CHAPTER 1 – INTRODUCTION

1.1. Immunisation

Immunisation is the most effective and successful public health intervention in the world for saving lives and promoting good health, right after clean water (1).

Vaccination began in 1796 with Edward Jenner's experiments (2). Jenner tested whether the deliberate inoculation of cowpox material would prevent the pustules caused by subsequent inoculation, which would be a sign of protection against the disease (3). The success of this experiment led Jenner to speculate that 'the annihilation of the smallpox, the most dreadful scourge of the human species, must be the final result of this practice' (3).

Rabies vaccine was developed using the principle of attenuation by Pasteur and first tested in man in 1885 (4). This vaccine was based on material obtained from infected rabbit brain attenuated by drying, an uncertain process, and vaccines prepared in this way frequently caused serious side effects (4). Most human rabies vaccines are now based on inactivated virus grown in tissue culture (4). Acquisition of the ability to grow viruses in tissue culture led to the development of attenuated vaccines against measles and poliomyelitis in the 1950s and the 1960s (4). Many other vaccines have been developed using the principle of attenuation, including rubella, influenza, rotavirus, tuberculosis and typhoid vaccines (4).

By the late 1959s, the majority of children in developed countries were receiving routine vaccination with tetanus toxoid, diphtheria toxoid and a killed pertussis vaccine (DTP) and polio vaccine and, in some countries, vaccination against tuberculosis (4). By the 1960s, the vast majority of deaths and severe illnesses attributable to vaccine preventable diseases were occurring in children in the developing world (4). At this time, about one-third of African children did not reach the age of 5 years and infectious diseases, particularly measles, accounted for a substantial proportion of these deaths (4).

While the concept of vaccination spread rapidly throughout the world, it was not until the Intensified Smallpox Eradication Program of 1967 that much progress was made in controlling the disease on a large scale (5). Massive vaccination campaigns occurred worldwide and were combined with sophisticated surveillance systems to detect outbreaks (5).

The implementation of routine and mass vaccination programmes has led to the eradication of smallpox, the last naturally occurring case of smallpox was in 1977, this infectious disease was known for plaguing millions of children globally (6–8). And to the elimination of poliomyelitis in many regions of the world, according to WHO the European Region was declared free of endemic polio in 2002 (9). Poliomyelitis is a devastating disease which paralyses children for life and until now, we did not find its cure (10). But it's been proven by experience that the vaccine against poliovirus is very effective and protects children for life

(10). In 1988 more than 350 000 children were paralysed by the disease, in more than 125 countries (10). In 2015 type 2 poliovirus was considered globally eradicated and there was a 3-year absence of type 3 poliovirus (9). Wild poliovirus type 1 is now cornered in only two remaining endemic countries – Afghanistan and Pakistan (9). However, in 2015 two cases of circulating vaccine-derived poliovirus were detected in the European Region, in Ukraine (9). This raises concerns over the safety of the population, high immunization coverage in all countries is crucial to keep the region polio free (9).

The implementation of routine and mass vaccination programmes allowed as well the control of once life-threatening diseases like diphtheria and tetanus (5–8).

A growing knowledge on immunology and the development of new technologies (recombinant DNA and conjugation of polysaccharides) to produce vaccines has increasingly influenced vaccine design in the past century and allowed the introduction of immunization programmes against hepatitis B, *Haemophilus influenzae* b, and pneumococcal and meningococcal diseases in many countries of the world (6,11).

Approximately 13 million of people in the WHO European Region are chronically infected with hepatitis B, leading to approximately 60 000 deaths per year from hepatitis-B-related liver cancer and cirrhosis (9). The prevention and control of this disease can be tracked through integrated programmes (9). Though national policies vary widely, 47 of 53 (87%) countries in the WHO European Region have successfully implemented universal hepatitis B immunization (9). This will lead in the long term to reduction of incidence and mortality due to acute hepatitis B, and consequences of chronic infection such as liver cirrhosis and hepatocellular carcinoma (9).

The efforts of countries and international agencies to increase vaccination coverage have produced notable results (6).

1.2. Vaccines

After a great scientific advance in terms of efficacy and safety, vaccines are nowadays considered to be an heterogeneous class of medicinal products containing immunogenic substances capable of inducing specific, active and protective host immunity against infectious disease (12). When these immunogenic substances are introduced in the organism it triggers a complex cascade of biological events, similar to real infection caused by an infectious agent which culminates in the production of antibodies against the antigen and the establishment of protective immunity and immunological memory against the pathogen (13,14).

During the first interaction of the immune system with the pathogen, lymphocyte activation and generation of memory cells are slow (3 to 14 days) and unspecific (15,16). Vaccination is used to induce this primary response of the immune system to a specific pathogen, in a secure and controlled environment (15,16). Specific memory cells to that pathogen are produced after

vaccination uptake and the organism will be protected against secondary infections caused by the same infectious agent in the vaccine (15,16).

When the immune system is exposed to an antigen against which there was a primary response mediated by a vaccine or disease, there is already a population of B-lymphocytes capable of recognizing this specific antigen due to the memory cells that were generated during the primary response (15,16). Memory B cells rapidly divide to produce plasma cells and a large amount of antibodies, the dose of antigen required to induce the response is lower than in the first response (15,16). So, the secondary response provides better protection than the primary response since the time required to start producing antibodies is lower (hours to few days) and because the amount of antibodies produced is much higher (15,16). The memory response also includes the formation of new memory B cells that protect the organism against further exposure to the antigen (15,16). Memory B cells can last for many years and in some cases a lifetime (15,16).

Infectious diseases are usually communicable diseases caused by an external agent such as virus, bacterium or parasite (14).

Vaccines for human use include one or more of the following: microorganisms inactivated by chemical and/or physical means that retain appropriate immunogenic properties; living microorganisms that have been selected for their attenuation whilst retaining immunogenic properties; antigens extracted from microorganisms, secreted by them or produced by recombinant DNA technology; chimeric microorganisms; antigens produced in vivo in the vaccinated host following administration of a live vector or nucleic acid or antigens produced by chemical synthesis in vitro. The antigens may be in their native state, truncated or modified following introduction of mutations, detoxified by chemical or physical means and/or aggregated, polymerized or conjugated to a carrier to increase immunogenicity. Antigens may be presented plain or in conjunction with an adjuvant, or in combination with other antigens, additives and other excipients (12).

Some of these antigens are weakly immunogenic and require the presence of adjuvants for the induction or enhancement of an adequate immune response (17,18). Adjuvants are compounds that enhance the immunogenicity of highly purified or recombinant antigens, it can be used thus to reduce the amount of antigen or the number of immunizations needed for protective immunity, to improve the efficacy of vaccines in newborns, the elderly or immunocompromised people, or as antigen delivery systems for the uptake of antigens by the mucosa (17,18).

Nowadays, vaccine adjuvants include aluminium saults, oil-in-water emulsions, monophosphoryl lipid A (MPL) and virosomes (19).

Aluminium adjuvants used in some vaccines include aluminium hydroxide, aluminium phosphate, alum (potassium aluminium sulphate), or mixed aluminium salts (20). Aluminium

adjuvant containing vaccines have a demonstrated safety profile of over six decades of use and have only uncommonly been associated with severe local reactions (20). The Food and Drug Administration (FDA) analysis indicates that the body burden of aluminium following injections of aluminium-containing vaccines never exceeds safe USA regulatory thresholds based on orally ingested aluminium even for low birth-weight infants (21). The most common source of exposure to aluminium is from eating food or drinking water (20).

Thimerosal is a mercury-containing organic compound, it is metabolized or degraded to ethylmercury and thiosalicylate (22). Since the 1930s, it has been widely used as a preservative in a number of biological and drug products, including many vaccines, to help prevent potentially life threatening contamination with harmful microbes (22). Thimerosal concentration as a preservative in a vaccine is 0.01%, which contains approximately 25 micrograms of mercury per 0.5 mL dose (22). For comparison, this is roughly the same amount of elemental mercury contained in a 85 gram can of tuna fish, although the bioavailability of mercury in the second case is lower (22).

The use of mercury-containing preservatives has declined in recent years due to the development of new products formulated into single-dose presentations that do not require preservatives (22). In Portugal, vaccines used in the National Immunization Program do not contain thimerosal (23).

1.3. National Immunisation Program

National Immunisation Programmes (NIP) adopted worldwide are important tools to protect the population against infectious disease (24). NIP are universal and delivered to every citizen from birth, free of charge (24).

The risk of contracting an infection caused by a pathogen is mainly related to 3 factors: the number of infected subjects in a population who are able to transmit the pathogen; the amount and type of contact between the ones who transmit and the ones who receive the pathogen; and the infectiousness of the pathogen (25). So, in order to control and eliminate *vaccine-preventable diseases* (VPD) high vaccine uptake is crucial (25). Vaccination not only provides direct individual protection, it also provides indirect population effects, protection of unvaccinated people in the population (25). If a sufficient proportion of a population has been vaccinated, protection is also provided to those who have not been vaccinated, for example due to a medical condition, this protection is known as *herd immunity* (26). This means that the success of any immunisation programme depends on meeting herd immunity levels to prevent local outbreaks and epidemics of the diseases it is targeting (1).

In the 1950s and 1960s Portugal was facing high mortality levels caused by tetanus and diphtheria diseases, causing 2625 and 1457 deaths respectively from 1956 to 1965 (27). Tetanus is a serious disease caused by an endotoxin produced by *Clostridium tetani* (28).

Tetanus natural infection does not confer immunity to the host, immunity can only be achieved by tetanus vaccination with tetanus toxoid (28). It is not possible to obtain herd protection from tetanus vaccination, so the only way to eliminate the disease is to adequately vaccinate 100% of the population (28). In 1962 tetanus and diphtheria vaccines become compulsory for all individuals living in Portugal, the *decree-law n.º 44198, 20th February* also specified that no individual under 10 years old could be accepted to educational establishments, and no individual could be accepted to public functions unless they prove to be vaccinated against diphtheria and tetanus (29). After diphtheria and tetanus vaccines have been made compulsory, there was a significant drop in mortality rate, from 1999 to 2008 tetanus caused 30 deaths and diphtheria caused 0 deaths (27).

In 1965 NIP was initiated in Portugal with a mass campaign against poliomyelitis, this was a devastating disease which caused child paralysis and death (30).

In 1966 Portugal's NIP included polio, tuberculosis, smallpox, pertussis, diphtheria and tetanus vaccines (30). Since 1952 there have been no cases of smallpox in Portugal, so in 1977 *Decree-Law n.º 19/77* was made public and smallpox vaccine was suspended (31). NIP's effectiveness is proven by the eradication of smallpox in 1980, the elimination of poliomyelitis throughout all European Region in 2002 and by the control of diphtheria, measles and neonatal tetanus in Portugal (30).

In 1974 measles' monovalent vaccine was included in the NIP, later in 1987 the monovalent vaccine was substitute by MMR vaccine which combined measles, mumps and rubella in the same vaccine (32). Initially, vaccine coverage was not enough to prevent an epidemy in 1987-89 with approximately 12.000 notified cases and 30 deaths (32). Europe was facing measles outbreaks in several countries, so in 2008 and 2011 complementary vaccination measures were reactivated and the epidemiological surveillance of measles was reinforced (32). Measles vaccine coverage in 2015 was 98% for 2014, 2013 and 2001 cohorts (33). Although vaccine coverage is very high in Portugal, in April 2017 there was a measles outbreak with 46 notified cases, 21 cases were confirmed and one adolescent died, 57% of confirmed cases occurred in unvaccinated people (34). This raises a big concern over the importance and necessity of immunising children according to NIP.

The Portuguese NIP includes eleven vaccines which are recommended to every child under 18 years old, against: hepatitis B (HBV), diphtheria, tetanus (Td), pertussis (DTPa), poliomyelitis (IPV), infections caused by *Haemophilus influenzae* serotype b (Hib), *Streptococcus pneumoniae* (13 serotypes), Meningococcal disease C (MenC), measles, mumps and rubella (MMR) (35). It is also recommended the vaccine against Human Papillomavirus to girls (35).

Since June 2016, Bacillus Calmette-Guérin (BCG) vaccine against tuberculosis is no longer universally recommended from birth, it is now recommended just to risk groups (35).

BCG is effective in preventing severe, rapidly progressive tuberculosis in children but does not prevent infection or re-activation of latent disease, and has had little impact on tuberculosis disease control worldwide (36).

HBV is the first recommended vaccine to be administered, the vaccine is administered in the maternity to the new-born (35). At 2-months old it is recommended administration of DTPa 1st dose, Hib, IPV and HBV 2nd dose – hexavalent vaccine DTPaHibIPVHBV (35). It is also administered the 1st dose of the combined vaccine against *Streptococcus pneumoniae* 13 serotypes – Pn13 (35). At 4-months old it is recommended DTPa, Hib and IPV 2nd dose – combined in a pentavalent vaccine DTPaHibIPV (35). And it is administered Pn13 2nd dose (35). At 6-months old it is recommended DTPa, Hib, IVP and HBV 3rd dose – hexavalent vaccine DTaPaHibIPVHBV (35). At 12-months old it is recommended Pn13 3rd dose, MenC and MMR 1st dose (35). At 18-months old it is recommended DTPa, IPV and Hib 4th dose - pentavalent vaccine DTPaHibIPV (35). At 5 years old it is recommended DTPa and IPV 5th dose – tetravalent vaccine DTPaIPV; and MMR 2nd dose (35). At 10 years old, it is recommended tetanus and diphtheria – Td, booster dose. It is recommended to girls 2 doses of HPV vaccine – HPV9 (0,6 months schedule) (35). Booster doses of tetanus and diphtheria are recommended at 10, 25, 45, 65 years old and every 10 years thereafter (35).

The evaluation of NIP is presented through the rates of vaccination coverage, the percentage of immunised population (serologic data) and the impact of vaccination on target disease (35). Although vaccine coverage in Portugal is considered high and the diseases are controlled, national authorities are aware of anti-vaccination movements which are emerging in the European Region, as for example in the Netherlands (30,37). To maintain this success, continued high coverage and trust in vaccination by the population is of the utmost importance (37).

The National Immunization Program in the Netherlands includes vaccination against the same twelve infectious diseases as it happens in Portugal (diphtheria, poliomyelitis, pertussis, tetanus, *Haemophilus influenzae* type b, meningococcal group C disease, measles, mumps, rubella, hepatitis B, pneumococcal disease, and cervical cancer caused by human papilloma virus) (38). All children below the age of 13 years are eligible to receive vaccinations included in the NIP (37). Routine vaccination started in the Netherlands in 1957, it is non-mandatory and free of charge (37). Incidence rates of nearly all diseases targeted by the Dutch NIP have been reduced successfully (37).

Although a variety of unknown factors may be behind vaccine coverage decline, parental vaccine hesitancy may be playing an important role in this field. It is important to understand what are the reasons and beliefs behind parent's decision to refuse one or more vaccines included in the NIP, so that we can find tools to increase vaccine confidence and maintain high vaccination coverage. Understanding parent's willingness to vaccinate their child, and the

reasons behind their choice is complex (26). Some parents may unquestioningly accept or reject all vaccination programme or just refuse some vaccines, while others experience uncertainty, which may delay or result in rejection of immunisation and some experience barriers that prevent immunisation (26).

1.4. Vaccine Evaluation

Any substance that is capable of producing a therapeutic effect can also produce unwanted or adverse effects (39). No drug which is pharmacologically effective is entirely without hazard (40).

A higher standard of safety is expected of vaccines, since vaccines are generally given to healthy subjects to prevent disease and not to cure it. Public tolerance of adverse reactions related to products given to healthy persons, especially risk groups – healthy infants and children, is substantially lower than for reactions to products administered to people who are already sick (41). This lower tolerance of risk for vaccines translates into a need to investigate the possible causes of very rare adverse events following vaccinations (41).

All authorized vaccines in the European market are rigorously tested and monitored, have high safety, efficacy and quality standard and it is also required certification to every batch manufactured prior to its distribution (35,42). Vaccines are among the safest medicinal product in use (42). Millions of vaccinations are administered to children each year (42). Serious adverse reactions are uncommon and deaths caused by vaccines are very rare (42).

ADR are a significant cause of morbidity and mortality especially among young children and are associated with significant healthcare costs (43). Most ADR are due to common drug used in everyday practice like antibiotics and nonsteroidal anti-inflammatory drugs, with up to 98% being considered preventable (43).

The regulation of vaccines can be divided into three stages: developmental, licensure and post-licensure (44).

The developmental stage consists of two parts, nonclinical research and development, and clinical research and development (44).

Nonclinical research refers to all in vivo and in vitro testing performed before and during the clinical development of vaccines, it includes all aspects of testing product characterization, proof of concept/ immunogenicity studies and safety testing in animals conducted prior to clinical testing of the product in humans (12). When safety testing in animals is preformed, there should be a clear rationale for doing so and the study should be performed in compliance with the national and international laws for the protection of laboratory animals, biosafety requirements and with good laboratory practice (12). Potential safety concerns for a vaccine product include those due to inherent toxicities of the product, toxicities of impurities and contaminants, and toxicities that result from interactions between the vaccine components

present in the vaccine formulation (12). In addition, the immune response induced by the vaccine may lead to toxic side-effects (12).

Clinical research and development main objective it to accumulate adequate data to support initial licensure and appropriate use, it will reflect how much is already known about the antigenic components and adjuvants in the vaccine (45). The essential elements of the pre-licensure clinical development programmes are: to describe the interaction between the vaccine and the host immune response; to identify safe and effective dose regimens and schedules; to estimate vaccine efficacy by directly measuring efficacy and/ or to provide evidence of vaccine efficacy based on immune responses; to describe the safety profile; and to assess co-administration with other vaccines if relevant (45).

After initial licensure, it is essential to monitor vaccine safety in routine use, studies designed to address specific safety issues that were identified as potential concerns from pre-licensure trials may need to be conducted, it is commonly appropriate to evaluate vaccine effectiveness (45). Further trials may be conducted and the data may be used to extend or to otherwise modify the use of the vaccine through revision of the prescribing information (45).

1.5. Pharmacovigilance System

According to WHO, “Pharmacovigilance is the science and activities related to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems” (46). The aim of pharmacovigilance is to improve patient care and safety related to drug use and medical interventions; contribute to the assessment of benefit, harm, effectiveness and risk of medicines; encouraging drug safe, rational and effective use; and promote understanding, educational and clinical training in pharmacovigilance and its effective communication to the public (46).

ADR spontaneous notification is an important tool in pharmacovigilance monitoring, the main objective of a spontaneous reporting system is to signal new ADRs, that have not been recognised prior to marketing, as soon as possible (47). In Portugal, physicians, pharmacists, nurses and other healthcare professionals, pharmaceutical industries and patients are able to report suspected ADR to the pharmacovigilance system (40).

ADR notification constitutes the base of the National Pharmacovigilance System (NPS) (35). The Portuguese NPS was created in 1992 through the Normative Order 107/ 92 of 27th June, its main objective is the early identification of possible safety concerns related to drug uptake, including vaccines (35,48,49). In 2000 the decentralization of NPS took place, and the Regional Pharmacovigilance Units (RPU) were created, this made possible a better interaction with reporters and a better disclosure of the NPS, contributing to a gradual increase in the number of suspected adverse reactions reports over the years (35). The number of ADR notifications received by the National Pharmacovigilance System (NPS) has been increasing

since 1992, this reflects the results of educational interventions developed by the Regional Pharmacovigilance Units (RPU) (40).

NPS is coordinated by Drug Risk Management Group of INFARMED, I.P., which is responsible for the reports monitoring from RPU, Health institutions, pharmaceutical industries, health professionals and general public (35). INFARMED reports serious and non-serious ADR reported cases occurred in Portugal to the European database for suspected ADR reports – EudraVigilance, and to WHO data base (35). Rapid alert European System allows withdraw of a vaccine batch which may have safety problems, in just 24 hours from all European Union (35). Vaccine Lack of efficacy should be notified as well because it can originate a public health issue (35).

When a serious adverse reaction report is received by INFARMED, all information is evaluated by an expert team on drug safety to verify if that adverse reaction may have occurred due to vaccine administration (35). Whenever safety issues are identified, adequate measures are applied, including information changes in the Summary of Product Characteristics (SmPC) and Package Leaflet (PL), elaboration of educational material, national market vaccine suspension or removal (35).

In the European Region, European Medicines Agency (EMA) is responsible for the scientific evaluation, supervision and safety monitoring of medicines developed by pharmaceutical companies for use in the Europe (50). The Pharmacovigilance Risk Assessment Committee (PRAC) is the EMA's committee responsible for assessing and monitoring the safety of human medicines (51). PRAC evaluates the safety signals detected in EudraVigilance and may recommend regulatory action as a result (51).

In the Netherlands, passive surveillance system is managed by the National Centre for Pharmacovigilance Lareb, it receives reports of AEFI for all vaccines included in the NIP (38). In 2015, Lareb received 1494 reports of a total of AEFI (38). Compared with 2014, this is an increase of about 50% (38). Of the reports, 130 were classified as serious (38). Whether this was a 'true' increase in the occurrence of AEFI or merely an increase in reporting rate is not known.

1.6. Parental Vaccine Hesitancy

According to *Strategic Advisory Group of Experts on Immunisation* (SAGE), measles and rubella elimination is progressing slower than expected. Since 2010, global measles incidence has decreased by 21% from 50 cases per million to 39.3 in 2015 which is substantially higher than the global 2015 target (<5 cases per million population) (52). Measles outbreaks have occurred in numerous countries as a result of sub-optimal immunisation coverage, along with increased susceptibility in older age groups (52).

Parental attitudes, experiences and social grade are influential in determining whether a child receives a vaccine (53). Parental knowledge of VPD influence their perception about the seriousness of diseases and the likelihood of their children being affected (53).

According to *Evans et al.*, parents conduct an informal risk-benefit analysis when deciding to immunise their child. Since records of vaccine preventable diseases cases are very low due to the success of immunisation programs, for some parents, it is easier to accept the risk of their child naturally contracting a disease than hurting their child through vaccination (54).

Most parents decide to vaccinate their children although they still have questions or concerns about childhood vaccines and the National Immunisation Program (55).

For many parents concerns about the safety, necessity and benefits of recommended vaccines result in the adoption of an alternative vaccination schedule that differs from the childhood vaccination schedule recommended by the *Centres for Disease Control and Prevention* for their children, and sometimes it can result in refusal of some or all vaccines (56,57). Use of alternative vaccination schedules leads to under immunization and has been shown to increase significantly the risk of contracting and spreading vaccine-preventable disease (56).

1.6.1. Anti-vaccination movements

One potential obstacle to parents vaccination intention is the popularity of anti-vaccine conspiracy theories (58).

In 1998, a paper in *The Lancet* described a small group of children experiencing developmental regression, including autism, and gastrointestinal problems (59). Andrew Wakefield's article was responsible by raising a massive wave of concerns among parents toward MMR vaccine in many regions of the world (58). Wakefield's association between MMR vaccine and two serious illnesses: inflammatory bowel disease and autism, led many parents to refuse this vaccine (59). A further article made additional claims that MMR vaccine was never properly tested (60). Although the majority of the authors of the original scientific paper linking MMR, autism and inflammatory bowel disease published a retraction of this interpretation and it has been proven that this study was false and that there was no scientific evidence to support the link between MMR and autism, MMR vaccination rates lie well below the recommended 95% uptake (53,58). Since then, parental concerns about perceived vaccine safety issues have led increasing numbers of parents to refuse or delay vaccination for their children, although the research has since been discredited and the author is no longer permitted to practice medicine (58,61,62)

In 1999, concerns were raised in the United States of America (USA) regarding exposure to mercury following immunization with thiomersal-containing vaccines (21). Three ecological studies suggesting an association between thiomersal and neurodevelopmental disorders were found to be fraught with methodological flaws (21). In addition, the continuous increase in the number of cases of autism diagnosed in the USA despite removal of thiomersal from most vaccines strongly argues against a causal association (21). Recently published studies confirm that in all populations studied, including pre-term and low birth-weight babies, the half-life of ethylmercury in blood is between 3 and 7 days (21). The Global Advisory Committee on Vaccine Safety concluded that animal or human toxicity studies suggest that the levels of ethylmercury attained in the blood and brain from cumulative doses of vaccines do not reach toxic levels, making biologically implausible any relation between thiomersal in vaccines and neurological toxicity (21).

Many other anti-vaccine conspiracy theories have emerged in recent years such as the belief that large pharmaceutical companies and governments are covering up information about vaccines to meet their own sinister objectives (58). According to the most popular theories, pharmaceutical companies stand to make such healthy profits from vaccines that they bribe researchers to fake their data cover up evidence of the harmful side effects of vaccines, and inflate statistic on vaccine efficacy (58). Anti-vaccine conspiracy theories therefore reflect suspicion and mistrust of scientific research examining vaccine efficacy and safety (58). Beliefs or exposure to conspiracy theories, negatively influence parent's attitudes toward the dangers of vaccines and their subsequent decision to vaccinate their children (58).

Parental perception of vaccine safety play an important role in parental decisions to vaccinate their children (58). Many parents believe that vaccines have dangerous side effects, and that exposure to the disease itself would often be preferable to the vaccination (58).

Anti-vaccination ideals impact has exponentially grown on society due to current improvements on information sharing, the proliferation of vaccine information on the internet can both provide answers and raise concerns, and it can be difficult for parents to determine trustworthiness of online sources, such concerns could erode public confidence in vaccine safety (55).

Anti-vaccination movements have been showing a significant impact on vaccination intentions. Jolley & Douglas research suggests that beliefs or exposure to anti-vaccine conspiracy theories are associated with reduced vaccination intentions and it may present an obstacle to vaccine uptake (58).

In Portugal, it seems like there's no records or publications of an organized anti-vaccination movement like it happens in other European countries, as for example, Netherlands (63).

In the other hand, Netherlands has a well-known group of parents who refuse vaccination including Protestants living in what is called the Bible Belt region, which stretches from the southwest to the northeast of the country (64). The members of Reformed Congregations believe that vaccination is contrary to the providence of God (37). This group is at risk for epidemics as a result of socio-geographical clustering, which has been observed for polio, measles, mumps and rubella (37). Anthroposophics believe that experiencing some childhood diseases may contribute to strengthening body and mind (37). They are scattered throughout the Netherlands, but clustering in anthroposophic schools is present (37). In 2008, an outbreak occurred at several anthroposophical schools in the Netherlands and also in anthroposophical communities abroad (37).

Besides this well-known group of anti-vaccination activists, in the last two decades, a broader anti-vaccination movement has emerged, including homeopaths and adherents of natural and alternative medicine (65). They question the self-evidence with which government provides and promotes large-scale vaccination programs. Some argue that diseases such as measles could provide someone with greater resilience against diseases like cancer and allergies later in life (65). Others emphasise the negative effects of vaccines, they argue vaccines contain dangerous toxic chemicals and overwhelm the immune system of young children (65).

The aim of this study is to analyse adverse events following immunisation cases in the Portuguese paediatric population between 2012 and 2016. Vaccine tendency in Portugal was analysed with resource to vaccine coverage variation and the number of vaccine-preventable disease cases in paediatrics in Portugal. These records were compared to The Netherlands data. An European country, with proximal population compared to Portugal (10 324 611 population in Portugal, 17 018 408 population in The Netherlands 2016 (66)), where anti-vaccination movements are well-known.

The secondary outcome of this research will be achieved with a systematic review, being the objective to identify the reasons and factors behind parent’s decision to not vaccinate, delay or question one or more vaccines included in the National Immunization Program in high-income countries.

2. CHAPTER 2 – RETROSPECTIVE STUDY ON ADVERSE DRUG REACTION IN PAEDIATRICS TO DTPa AND MMR VACCINES IN PORTUGAL, FROM 2012 TO 2016

2.1. Introduction

According to European Medicines Agency's (EMA) Guideline on good pharmacovigilance practices, Adverse drug reaction (ADR) is all noxious and unintended responses to a medicinal product, a causal relationship between a medicine and an adverse event is at least a reasonable possibility (67). Adverse reactions may arise from the use of the product within or outside the terms of the marketing authorisation or from occupational exposure (67). Conditions outside the marketing authorization include off-label use, overdose, misuse, abuse and medication errors (67). According to DIRECTIVE 2001/83/EC, serious adverse reaction is defined as an adverse reaction which results in death, is life-threatening, requires in-patient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly/ birth defect (68).

ADR can be classified according to six different types (39,69). Type A (Augmented) reactions are dose-related, are predictable from the known pharmacology of a drug and are associated with high morbidity and low mortality (39,69). Type B (Bizarre) reactions are non-dose-related, idiosyncratic, bizarre or novel responses that cannot be predicted from the known pharmacology of a drug and are associated with low morbidity and high mortality (39,69). Type C (continuing) are related to both dose and time are associated to the cumulative dose, type D (delayed use) are delayed reactions, occurs or becomes apparent time after the use of the drug, type E (end of use) reactions are related to withdrawal effects, type F (Failure) reactions are unexpected failure of therapy, often caused by drug interactions (39,69).

An Adverse event following immunization (AEFI) is any untoward medical occurrence which follows immunization and which does not necessarily have a causal relationship with the usage of the vaccine (70). The adverse event may be any unfavourable or unintended sign, abnormal laboratory finding, symptom or disease (70). Serious AEFIs are those which are life-threatening, result in hospitalization or a prolongation of hospitalization, result in persistent or significant disability, or where the outcome is a birth defect or death (70). AEFI are grouped into five categories which are: vaccine product-related reaction (caused or precipitated by a vaccine due to one or more of the inherent properties of the vaccine product) , vaccine quality defect-related reaction (one or more quality defects of the vaccine product including its administration device as provided by the manufacturer), immunization error-related reaction (inappropriate vaccine handling, prescribing or administration and thus its nature is preventable), immunization anxiety-related reaction (AEFI arising from anxiety about the

immunization) and coincidental event (caused by something other than the vaccine product, immunization error or immunization anxiety) (70).

A ten-year study performed by Nogueira Guerra *et al.* showed that the most frequent ATC codes involved in suspected ADR, in a Portuguese paediatric population, were vaccines (n=842, 42%) and antibacterial for systemic use (n=336, 17%) (43).

The most frequent adverse events following immunisation (AEFI) are mild cutaneous reactions in the local site of the injection, fever and crying (35,38). Drugs, including vaccines, have been determined to rarely cause anaphylaxis (42). The risk of anaphylaxis is less than two cases per million doses of vaccines administered to children and adolescents (42). Although it is serious and can be fatal, death and other complications can be prevented with rapid treatment using effective medications including epinephrine, corticosteroids and beta-agonists (42).

Healthcare providers can take specific actions to help prevent adverse reactions, including proper screening for contraindications and precautions, and observing a 15-minute waiting period after vaccination to prevent fall-related injuries from syncope (42).

As vaccines are generally administered to healthy subjects, often young children, adverse reactions have a strong impact on the immunization acceptability as well as on its risk/ benefit balance assessment (71).

2.2. Aims

This study aimed to analyse a paediatric case series of ADR spontaneous reports to DTPa and MMR vaccines received by the Portuguese Pharmacovigilance System of the National Authority of Medicines and Health Products, (INFARMED, I.P.) between 2012 and 2016.

2.3. Methods

2.3.1. Data Source

For this study, ADR reports received by the National Pharmacovigilance System from 01.01.2012 to 31.12.2016 concerning individuals aged from birth to 18 years old exposed to diphtheria, tetanus and pertussis vaccine (DTPa), and/ or to measles, mumps and rubella vaccine (MMR) were requested to the INFARMED, I.P. Other vaccine combinations which includes DTPa or MMR vaccines were included for analysis. If the subject was exposed to multiple vaccines/ drugs at the same period, there can be more than one suspected medicine of adverse reaction, this explains why we include other vaccines than the selected ones.

The terminology used to code ADRs was based on the Medical Dictionary for Regulatory Activities (MedDRA). Medical terms are coded according to System Organ Classes (SOC)

affected. Where a single report included more than one adverse event classified under the same MedDRA SOC classification, these were treated as one adverse event.

ADR were characterized as serious if it corresponds to “any untoward medical occurrence that at any dose results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, or is a congenital anomaly/ birth defect, is a medically important event or reaction. Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above”.

The suspected drugs involved were presented as medicinal product’s name and characterized by therapeutic group according to the WHO Anatomical Therapeutic Chemical (ATC) classification system.

A single report may have more than one suspected medicinal product. In each report, the number of ATC accounted corresponds to the number of different suspected medicinal products. In this study, we did not receive information on causality assessment of the adverse drug reaction to estimate the strength of relationship between drug(s) exposure and the occurrence of adverse reaction(s).

2.3.2. Variables

The variables analysed in this study were:

- The number of adverse drug reaction notification by year of report;
- Patients demographics regarding age and gender;
- The source of notification, according to the region or entity (industry) from where it was reported, and the type of reporter (nurse, physician, pharmacist, pharmaceutical industry, patient);
- ADR report according to its SOC, one single report may refer to multiple ADR so the number of ADRs may be higher than the number of reports shown in the overview;
- MedDRA Preferred Term (MedDRA PT) of the reported adverse reactions for the most frequent SOC involved in the reports;
- ADR seriousness, associated criteria (hospitalization, congenital anomaly, disability, life threatening, other) and outcome;
- ATC codes of the suspected drugs of ADR reports.

2.3.3. Statistical Analysis

Descriptive statistical analysis was performed using SPSS ™ software. Relative and absolute frequencies were calculated.

2.4. Results

2.4.1. Adverse drug reaction reports to DTPa and MMR in paediatric population

From 2012 to 2016, a total of 591 ADR reports, concerning individuals in paediatric population (≤18 years old) exposed to diphtheria, tetanus and pertussis vaccine (DTPa), and/ or to measles, mumps and rubella vaccine (MMR), were received by the Portuguese Pharmacovigilance System. The 591 ADR reports analysed included a total of 1964 ADR, with an approximate average of 3,32 adverse reactions per report (figure 1). According to data, 2013 corresponded to the year with more number of DTPa and MMR related ADR reports (n=181), in 2012 a lower number of ADR were reported (n=86).

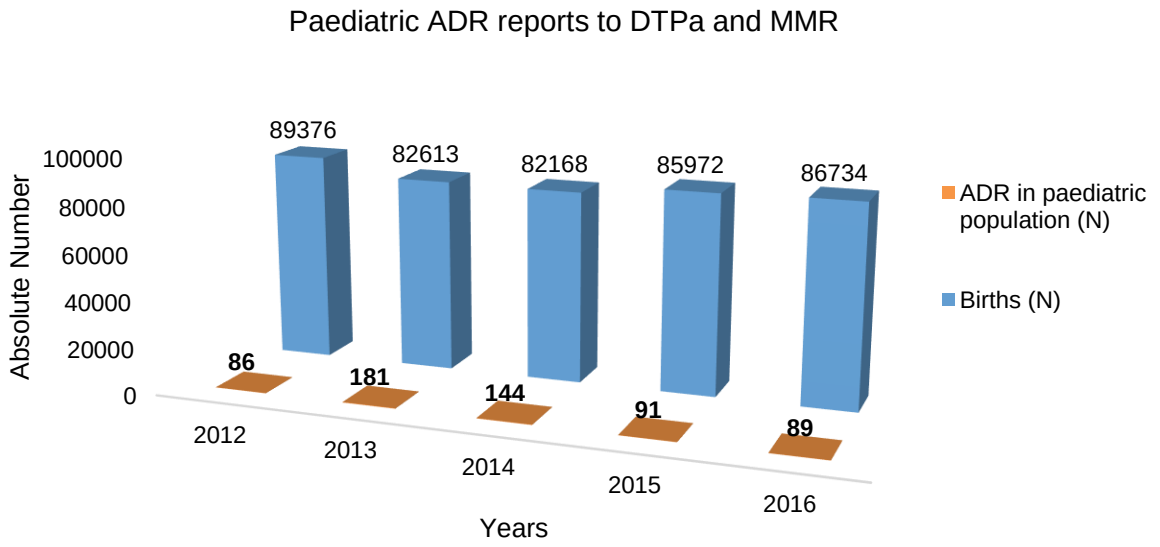

Figure 1. Number of adverse drug reactions (ADR) reports to diphtheria, tetanus and pertussis vaccine, and/ or to measles, mumps and rubella vaccine in paediatric population (≤18 years old) versus Portuguese number of births by year (estimated from birth rate according to Portuguese population) (72,73).

In the same period, a total of 22571 ADR spontaneous reports were received by the INFARMED, concerning all medicines (figure 2). From 2012 to 2016 the total number of ADR reports, concerning all medicines, is increasing. DTPa and MMR vaccines adverse drug reaction reports in paediatrics is suffering a decrease from 2013 to 2016. It represents 1,56% (2016), to 5,23% (2013) of the total ADR cases received by the INFARMED. According to this study, ADR reports to DTPa and MMR in paediatrics represent 43,58% (n=181) in 2013 of the total reports received by the INFARMED concerning vaccines class (ATC – J07), to 26,03% (n=89) in 2016 (figure 3).

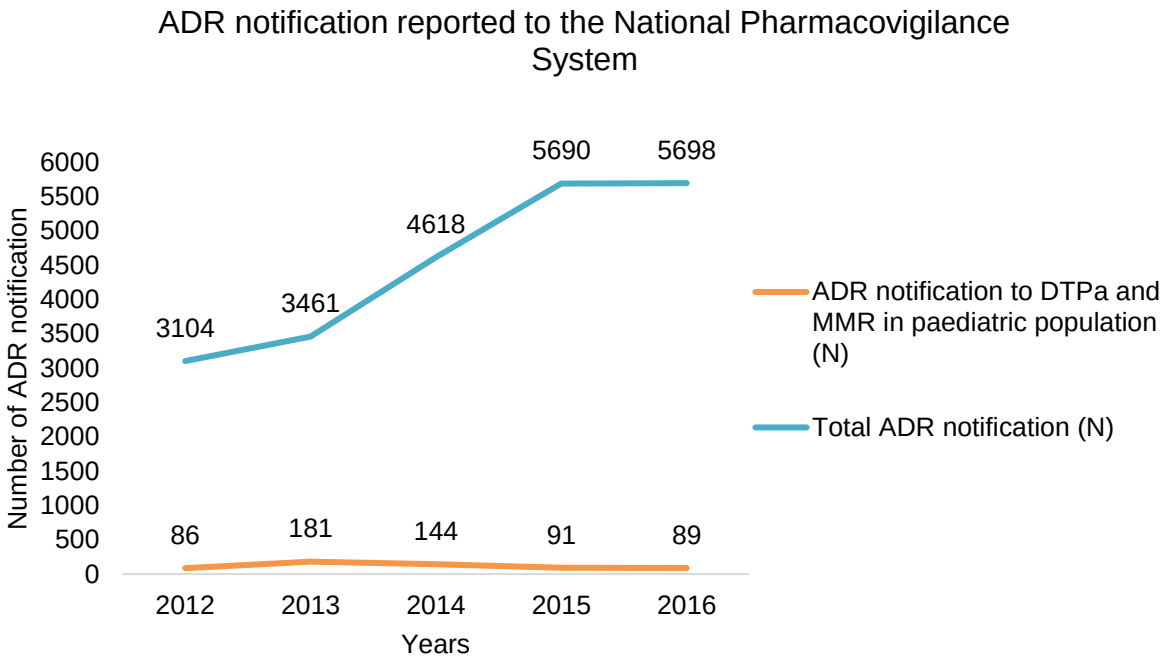

Figure 2. Number of adverse drug reaction notification to diphtheria, tetanus and pertussis vaccine, and/ or to measles, mumps and rubella vaccine in paediatric population (≤18 years old) versus total number of ADR notification reported to the National Pharmacovigilance System, from 2012 to 2016.

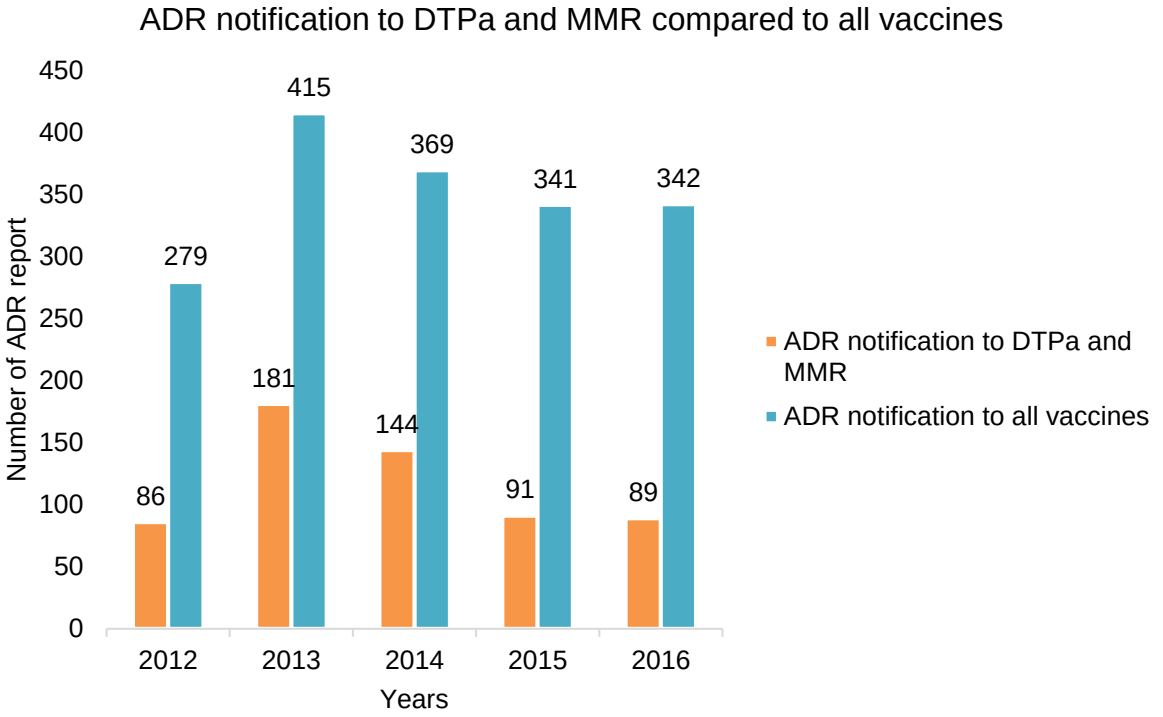

Figure 3. Number of adverse drug reaction notification to diphtheria, tetanus and pertussis vaccine, and/ or to measles, mumps and rubella vaccine in paediatric population (≤18 years old) compared to the total number of adverse drug reaction notification received by the INFARMED for all vaccines (ATC – J07).

2.4.2. Adverse drug reaction reports distribution according to the region of origin

According to this study, from the total of 591 ADR reports, 36,38% (n=215) were originated in the centre region, followed by Lisbon and Tagus Valley, 24,87% (n=147), and North, 22,34% (n=132). 1,35% (n=8) of the total ADR notification were directly reported by the industry (figure 4).

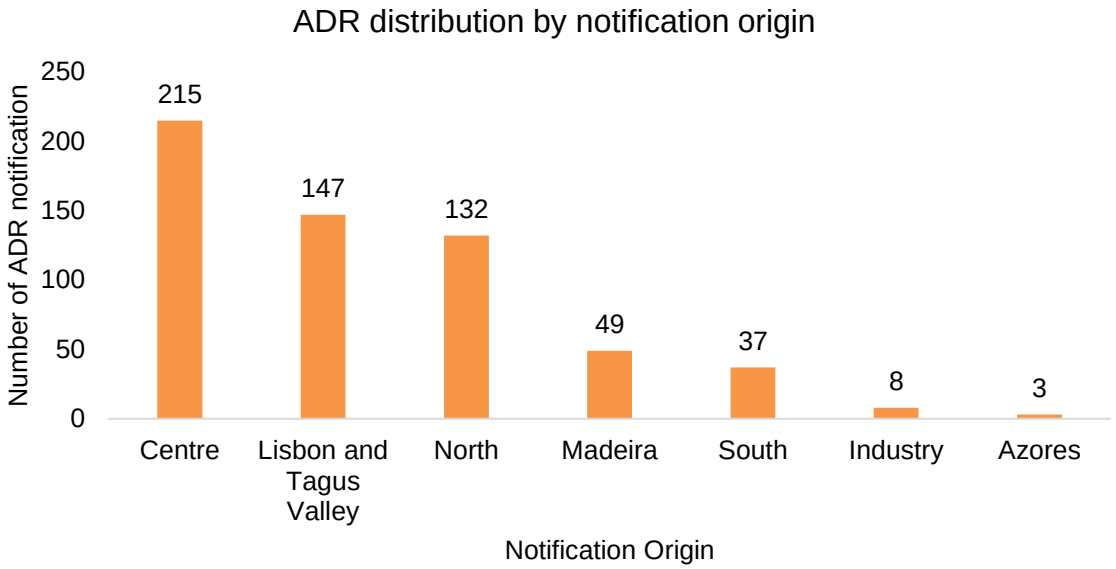

Figure 4. Adverse drug reaction notification to diphtheria, tetanus and pertussis vaccine, and/ or to measles, mumps and rubella vaccine in paediatric population (≤18 years old) according to notification origin.

2.4.3. Characterization of the affected patient

Population demographics were studied, the most predominant age group of the ADR reports in this study was from 3 to 12 years-old (54,7%, n=323), followed by age group 2 months to 3 years-old, (26,1%, n=154), 12 to 18 years-old (16,8%, n=99), 0 to 2 months (2,0%, n=12), in three the age was not described (table 1). The median age was 5 years old and the mode was 5 years old as well (standard deviation: 4,75 years). 57,5% of the total ADR reports occurred in male gender, and 42,1% in female, 2 ADR reports did not specify the gender of the individual. We found a male predominance throughout all age groups.

Table 1. Demographic information of the studied population. Individuals gender number and percentage distributed by age group.

		Gender			Total
		Unknown N (%)	Female N (%)	Male N (%)	**N (%)**
Age Group	Unknown	0 (0%)	1 (33,3%)	2 (66,7%)	3 (0,5%)
	[0-2m[	0 (0%)	5 (41,7%)	7 (58,3%)	12 (2,0%)
	[2m-3y[	1 (0,6%)	75 (48,7%)	78 (50,6%)	154 (26,1%)
	[3y-12y[	1 (0,3)	132 (40,9%)	190 (58,8%)	**323 (54,7%)**
	[12y-18y]	0 (0%)	36 (36,4%)	63 (63,6%)	99 (16,8%)
Total		2 (0,3%)	249 (42,1%)	**340 (57,5%)**	591 (100%)

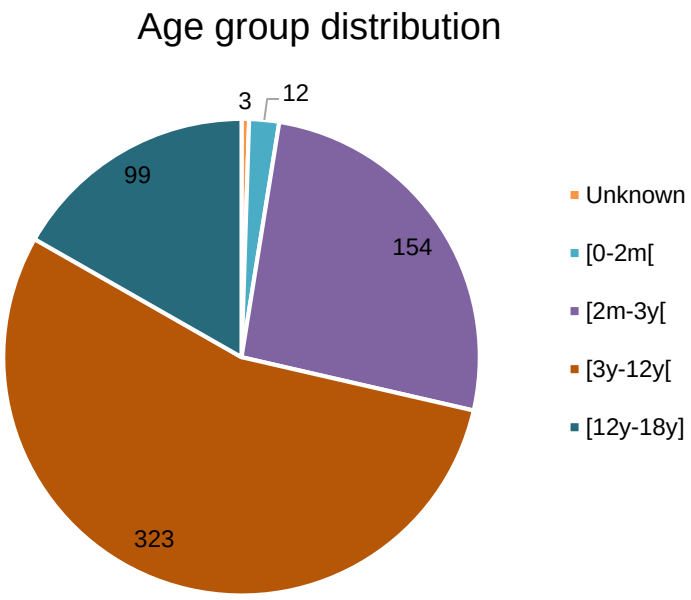

Figure 5. Age group distribution of the total 591 adverse drug reaction (ADR) reports.

2.4.4. Adverse drug reaction according to reporter profile

From the total of 591 ADR reports, the majority of reports were submitted by nurses (n=355, 60,1%), followed by physicians (n=218, 36,9%), pharmacists (n=9, 1,5%), other sources (n=6, 1%) and patient/ non-healthcare professionals (n=3, 0,5%) (figure 6). ADR reports concerning all medicines reported to the National Pharmacovigilance System from 2012 to 2016 shows a different distribution in terms of the type of reporter. In this case, the majority of reports were submitted by physicians, and the nurse occupies the third place in ADR reporting.

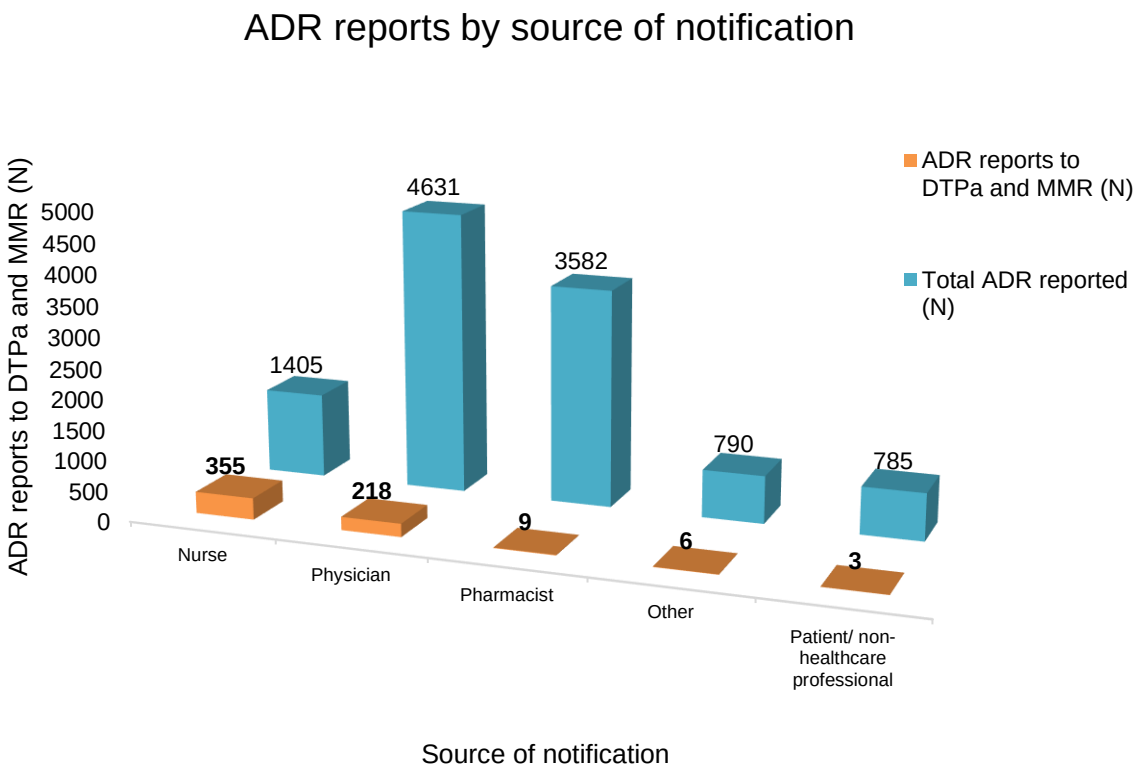

Figure 6. Adverse drug reaction reports to DTPa and MMR vaccines in the paediatric population versus the total of the adverse drug reaction reported to the National Pharmacovigilance System concerning all medicines in the same period (2012 to 2016), according to the type of reporter.

2.4.5. ADR report System Organ Class

The total 591 ADR reports analysed included a total of 1964 ADR, 21 different system organ class (SOC) were involved (table 2). In the same report, more than one reported reaction could correspond to the same SOC, in that case we just counted the corresponding SOC as one. The most frequently reported reactions were associated to general disorders and administration site conditions with 39,5% (n=475) of ADR, followed by injury, poisoning and procedural complications with 14,3% (n=172), infections and infestations 13,5% (n=162), gastrointestinal disorders 12,3% (n=148), skin and subcutaneous tissue disorders 8,1% (n=97).

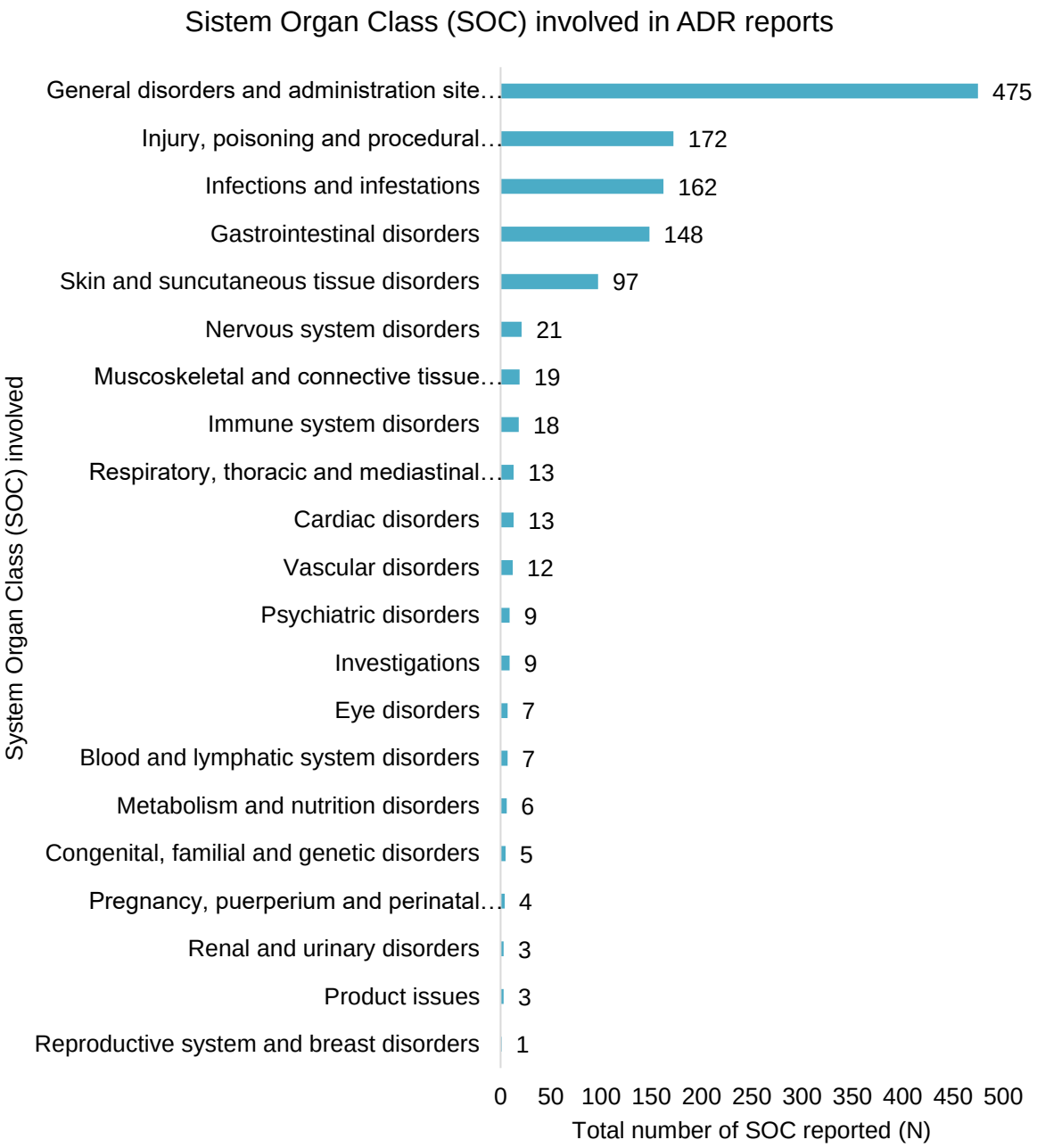

Figure 7. System Organ Class involved in the studied ADR reports.

The five most frequent SOC involved in the ADR reports were analysed in detail in table 2. MedDRA Preferred Term (MedDRA PT) was accessed for each different SOC, and the frequency of the reported reaction. It is important to note, that in a single report it is possible to find more than one MedDRA PT corresponding to the same SOC.

Table 2. Most frequent System Organ Class involved in the studied adverse drug reaction reports and its most frequent MedDRA Preferred Term.

System Organ Class/ MedDRA Preferred Term	Total Number of SOC reported (N)
General disorders and administration site conditions	**1093**
Pyrexia	139
Vaccination site oedema	117
Injection site erythema	100
Vaccination site erythema	85
Vaccination site warmth	66
Vaccination site pain	48
Drug ineffective	46
Injection site oedema	41
Vaccination site inflammation	41
No adverse event	34
Injury, poisoning and procedural complications	**191**
Vaccination failure	131
Vaccination error	20
Medication error	18
Drug administration error	6
Expired product administered	4
Inappropriate schedule of drug administration	4
Drug administered to patient of inappropriate age	2
Incorrect product storage	1
Incorrect route of drug administration	1
Wrong drug administered	1
Infections and infestations	**171**
Mumps	67
Pertussis	54
Vaccination site cellulitis	18
Cellulitis	7
Orchitis	4
Exanthema subitum	3
Parotitis	3
Vaccination site abscess	2
Viral infection	1
Viral parotitis	1
Gastrointestinal disorders	**162**
Parotid gland enlargement	123
Vomiting	10
Diarrhoea	6
Abdominal pain	5
Nausea	3
Salivary hypersecretion	2
Oral disorder	1
Oral mucosal eruption	1
Post-tussive vomiting	1
Rectal prolapse	1

Skin and subcutaneous tissue disorders	**152**
Erythema	45
Rash	19
Pruritus	17
Rash generalised	14
Oedema	8
Rash macular	8
Generalised erythema	5
Rash papular	5
Rash pruritic	3
Skin warm	3

General disorders and administration site condition corresponds to 55,65% (n=1093) of the total 1964 reported MedDRA PT. In this particular case, we just analysed the most frequent MedDRA PT corresponding to this SOC. The most reported MedDRA PT in this SOC was pyrexia with 7,08% (n=139) of the total 1964 reported MedDRA PT, followed by vaccination site oedema (5,96%, n=117), injection site erythema (5,09%, n=100), vaccination site erythema (4,33%, 85) and vaccination site warmth (3,36%, 66).

System organ class injury, poisoning and procedural complications, accounts for 9,73% (n=191) of the total 1964 reported MedDRA PT. The most frequent cited MedDRA PT in this SOC are vaccination failure (6,67%, n=131), vaccination error (1,02%, n=20), medication error (0,92%, n=18), drug administration error (0,31%, n=6) and inappropriate schedule of drug administration (0,20%, n=4).

Infection and infestation SOC is present in 8,71% (n=171) of the total 1964 reported MedDRA PT. The most reported MedDRA PT in this SOC are mumps (3,41%, n=67), pertussis (2,75%, n=54), vaccination site cellulitis (0,92%, n=18), cellulitis (0,36%, n=7), orchitis (0,20%, n=4).

Gastrointestinal disorder SOC occurs in 8,25% (n=162) of the total 1964 reported MedDRA PT. Parotid gland enlargement (6,26%, n=123) is the most cited MedDRA PT in this SOC, followed by vomiting (0,51%, n=10), diarrhoea (0,31%, n=6), abdominal pain (0,25%, n=5) and nausea (0,15%, n=3).

The fifth most frequent system organ class present in the analysed ADR reports was skin and subcutaneous tissue disorders, it accounts for 7,74% (n=152) of the total 1964 reported MedDRA PT. The most frequent MedDRA PT in this SOC are erythema (2,29%, n=45), rash (0,97%, n=19), pruritus (0,87%, n=17), rash generalised (0,71%, n=14) and rash macular (0,41%, n=8).

Table 3. System Organ Class (SOC) involved in ADR reports studied per age group.

System Organ Class (SOC) involved (N)	Age Group					Total N, (%)
	[0-2m[N (%)	[2m-3y[N (%)	[3y-12y[N (%)	[12y-18y] N (%)	Unknown N (%)	
General disorders and administration site conditions	5 (0,42%)	110 (9,14%)	284 (23,59%)	73 (6,06%)	3 (0,25%)	475 (39,5%)
Injury, poisoning and procedural complications	4 (0,33%)	31 (2,57%)	45 (3,74%)	92 (7,64%)	0 (0,00%)	172 (14,3%)
Infections and infestations	3 (0,25%)	31 (2,57%)	67 (5,56%)	61 (5,07%)	0 (0,00%)	162 (13,5%)
Gastrointestinal disorders	2 (0,17%)	19 (1,58%)	37 (3,07%)	90 (7,48%)	0 (0,00%)	148 (12,3%)
Skin and subcutaneous tissue disorders	1 (0,08%)	32 (2,66%)	64 (5,32%)	0 (0,00%)	0 (0,00%)	97 (8,1%)
Nervous system disorders	0 (0,00%)	12 (1,00%)	8 (0,66%)	1 (0,08%)	0 (0,00%)	21 (1,7%)
Musculoskeletal and connective tissue disorders	1 (0,08%)	3 (0,25%)	15 (1,25%)	0 (0,00%)	0 (0,00%)	19 (1,6%)
Immune system disorders	0 (0,00%)	8 (0,66%)	10 (0,83%)	0 (0,00%)	0 (0,00%)	18 (1,5%)
Cardiac disorders	2 (0,17%)	6 (0,50%)	5 (0,42%)	0 (0,00%)	0 (0,00%)	13 (1.1%)
Respiratory, thoracic and mediastinal disorders	3 (0,25%)	10 (0,83%)	0 (0,00%)	0 (0,00%)	0 (0,00%)	13 (1.1%)
Vascular disorders	0 (0,00%)	4 (0,33%)	8 (0,66%)	0 (0,00%)	0 (0,00%)	12 (1,0%)
Investigations	2 (0,17%)	3 (0,25%)	4 (0,33%)	0 (0,00%)	0 (0,00%)	9 (0,7%)
Psychiatric disorders	0 (0,00%)	7 (0,58%)	2 (0,17%)	0 (0,00%)	0 (0,00%)	9 (0,7%)
Blood and lymphatic system disorders	0 (0,00%)	4 (0,33%)	3 (0,25%)	0 (0,00%)	0 (0,00%)	7 (0,6%)
Eye disorders	0 (0,00%)	4 (0,33%)	3 (0,25%)	0 (0,00%)	0 (0,00%)	7 (0,6%)
Metabolism and nutrition disorders	1 (0,08%)	3 (0,25%)	2 (0,17%)	0 (0,00%)	0 (0,00%)	6 (0,5%)
Congenital, familial and genetic disorders	2 (0,17%)	2 (0,17%)	0 (0,00%)	1 (0,08%)	0 (0,00%)	5 (0,4%)
Pregnancy, puerperium and perinatal condition	1 (0,08%)	1 (0,08%)	0 (0,00)	2 (0,17%)	0 (0,00%)	4 (0,3%)
Product issues	0 (0,00%)	3 (0,25%)	0 (0,00%)	0 (0,00%)	0 (0,00%)	3 (0,2%)
Renal and urinary disorders	0 (0,00%)	2 (0,17%)	0 (0,00%)	1 (0,08%)	0 (0,00%)	3 (0,2%)
Reproductive system and breast disorders	0 (0,00%)	0 (0,00%)	1 (0,08%)	0 (0,00%)	0 (0,00%)	1 (0,1%)
Total (N,%)	27 (2,24%)	295 (24,50%)	558 (46,35%)	321 (26,66%)	3 (0,25%)	1204 (100,00%)

2.4.6. Adverse drug reaction seriousness

ADR reports were classified according to its seriousness (figure 8), from the total 591 ADR notifications, 55,33% (n=327) were considered serious. 43,73% (n=143) of serious ADR reports occurred in age group [3y-12y[. In age group [12y-18y], the total number of ADR reported (n=99, 30,28%) were considered serious.

Among the 327 serious ADR report, 13,46% (n=44) required patient hospitalization, 22 cases (50,00%) occurred in [3y-12y[age group, 7,34% (n=24) represented temporary or definitive disability, 2,14% (n=7) were considered life threatening, with 4 cases (57,14%) in [2m-3y[age group (figure 9). 64,53% (n=211) of patients that reported a serious ADR completely recovered, 1,22% (n=4) were classified as persistent without recovery, 8,87% (n=29) remain in recovery process, and there are 25,38% (n=83) cases with unknown records (figure 10).

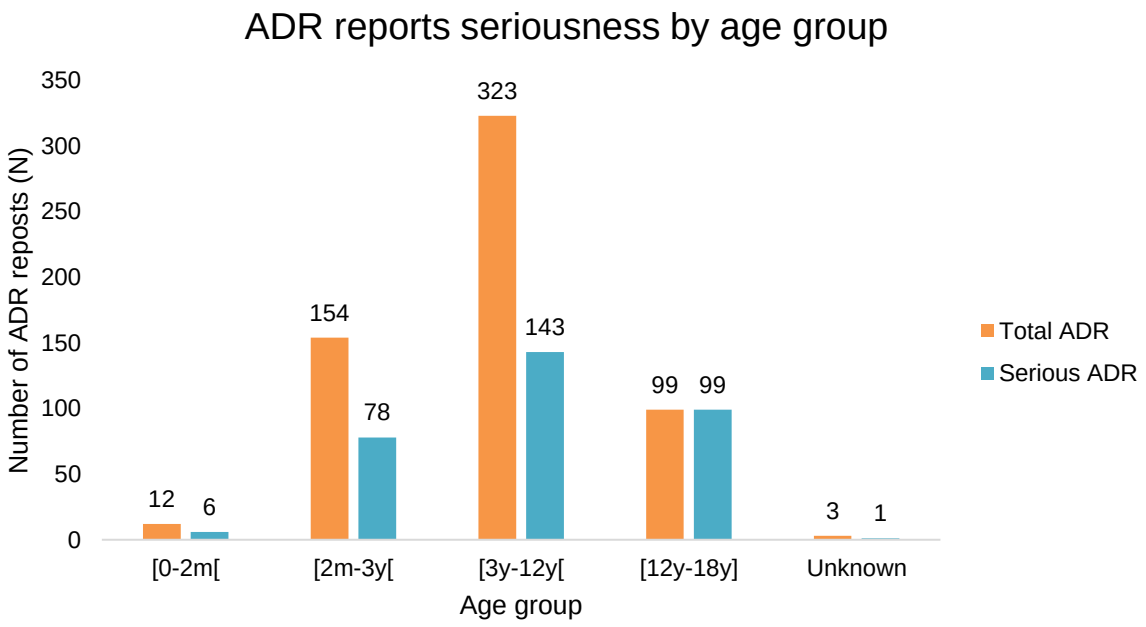

Figure 8. Adverse Drug Reaction (ADR) seriousness by age group.

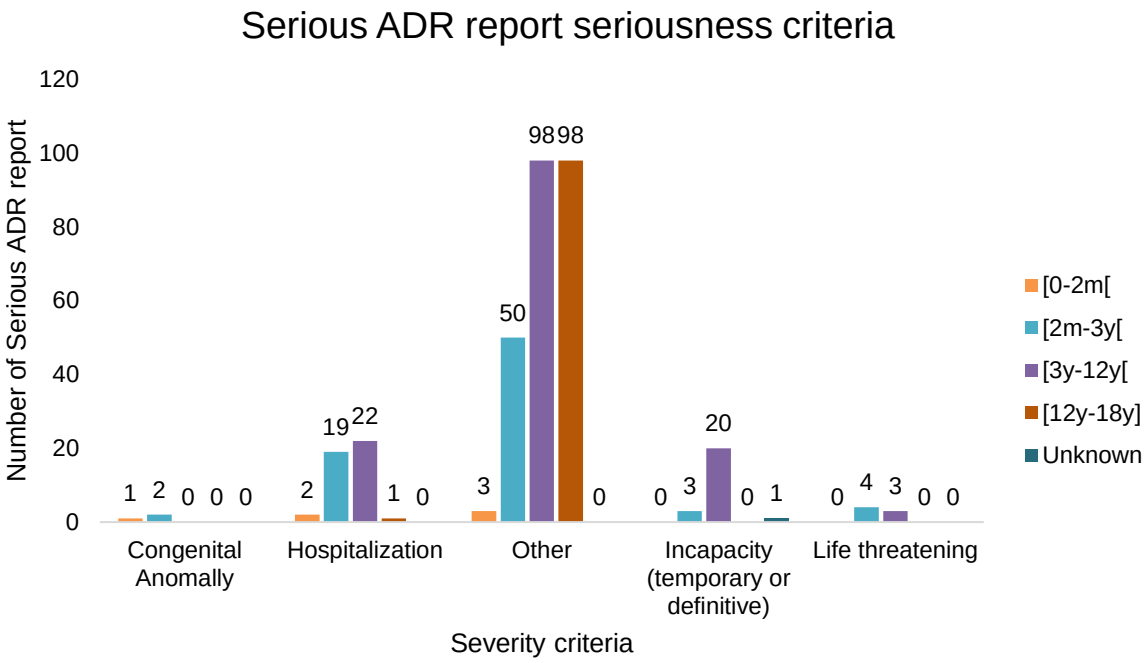

Figure 9. Serious Adverse Drug Reaction (ADR) report seriousness criteria by age group. The criteria "Other" represents ADR that are not included in the existing criteria due to its specificity, but it is considered medical important and usually requires medical intervention.

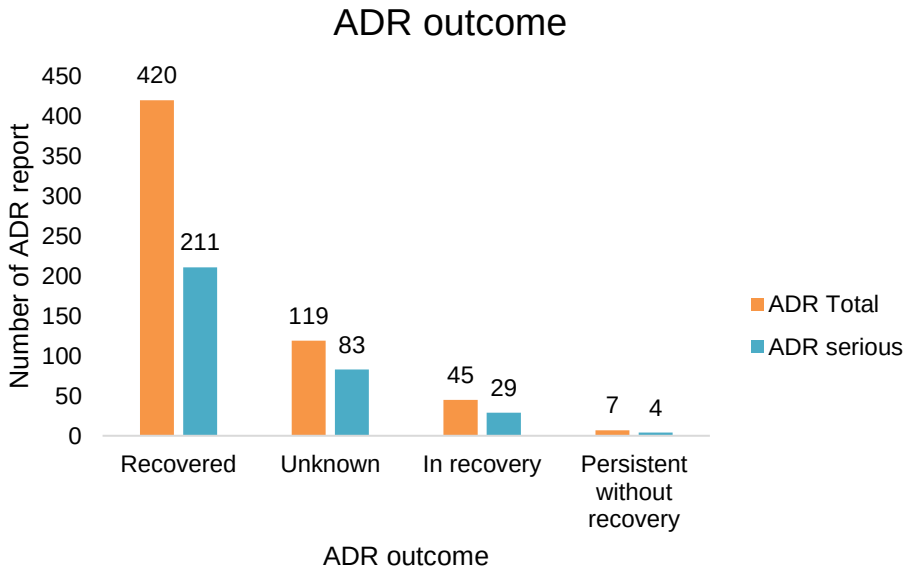

Figure 10. Total Adverse Drug Reaction (ADR) outcome versus serious ADR outcome.

2.4.7. Anatomical therapeutic chemical codes involved

Although this study focusses on adverse drug reactions to diphtheria, tetanus and pertussis vaccine, and measles, mumps and rubella vaccine, other drugs or vaccines may be involved in the ADR. From the 591 ADR reports, 20 different Anatomical Therapeutic Chemical

(ATC) codes were involved in suspected ADR (table 4). One report may present more than one suspected drug of adverse reaction, so ADR reports included a total of 761 ATC codes. We analysed ATC codes involved in suspected ADR in each age group. The most representative ATC code was J07CA02 diphtheria-pertussis-poliomyelitis-tetanus (35,48%, n=270), followed by J07BD52 measles, combinations with mumps and rubella, live attenuated (28,65%, n=218), J07AX Other bacterial vaccines (13,14%, n=100), J07CA06 diphtheria-haemophilus influenzae B-pertussis-poliomyelitis-tetanus (13,01%, n=99) and J07BC01 hepatitis B, purified antigen (2,63%, n=20). In age group [0-2m[the most frequent ATC code was J07CA06 diphtheria-haemophilus influenzae B-pertussis-poliomyelitis-tetanus (0,79%, n=6), in age group [2m-3y[was J07AX Other bacterial vaccines (8,15%, n=62) followed by J07CA06 diphtheria-haemophilus influenzae B-pertussis-poliomyelitis-tetanus (6,96%, n=53), in age group [3y-12y[was J07CA02 diphtheria-pertussis-poliomyelitis-tetanus (33,64%, n=256) and in age group [12y-18y] was J07BD52 measles, combinations with mumps and rubella, live attenuated (13,53%, n=103) (figure11).

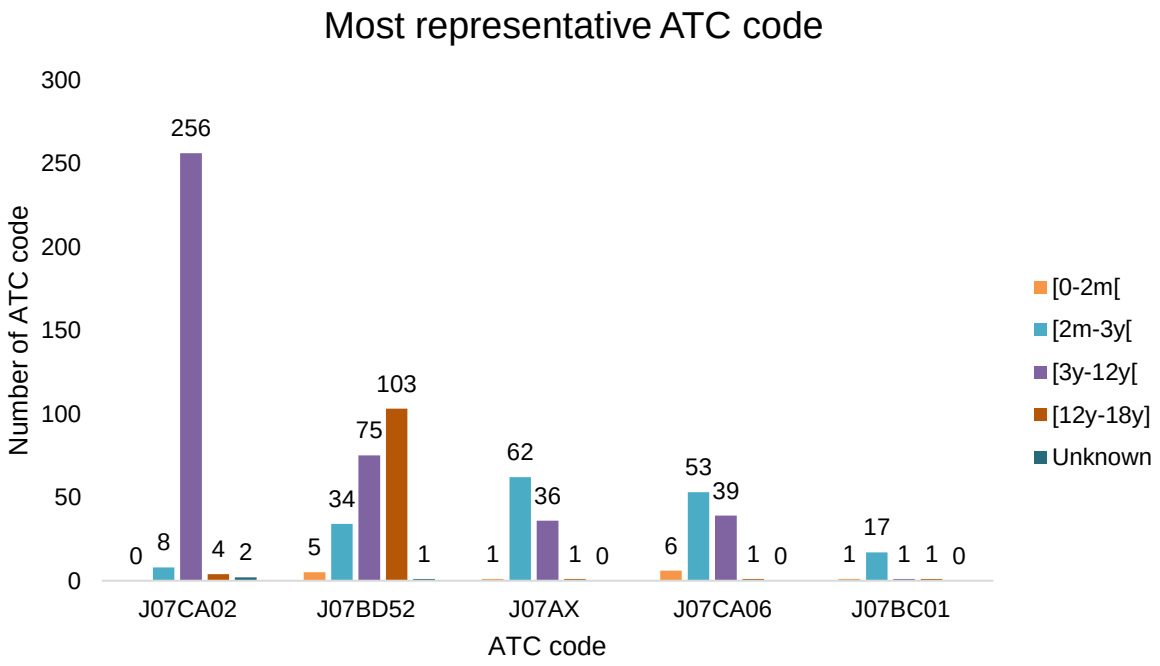

Figure 11. Five most representative Anatomical Therapeutic Chemical (ATC) codes per age group.

J07CA02 diphtheria-pertussis-poliomyelitis-tetanus

J07BD52 measles, combinations with mumps and rubella, live attenuated

J07AX Other bacterial vaccines

J07CA06 diphtheria-haemophilus influenzae B-pertussis-poliomyelitis-tetanus

J07BC01 hepatitis B, purified antigen

2.4.8. Suspected medicinal product's name of ADR report

Suspected drugs involved in ADR reports were analysed, although our study focus on diphtheria, tetanus and pertussis vaccine, and measles, mumps and rubella vaccine, if the subject was exposed to multiple drugs, it can originate more than one suspected drug of causing the reported adverse reaction, other than the selected ones. A total of 761 drugs were reported as suspected drug of adverse reaction (table 5). 28 different drugs were involved and 7 drugs were not specified.

The most frequent drug in ADR report was INFANRIX TETRA® vaccine (n=200, 24,8%), followed by M-M-RVAXPRO® vaccine (n=100, 12,5%), INFANRIX HIB (n=93, 11,6%), M-M-R® II vaccine (n=93, 11,6%), PENTAVAC® vaccine (n=78, 9,00%) (figure 12).

Our data lacks causality assessment of the adverse drug reaction to estimate the strength of relationship between drug(s) exposure and occurrence of adverse reaction(s).

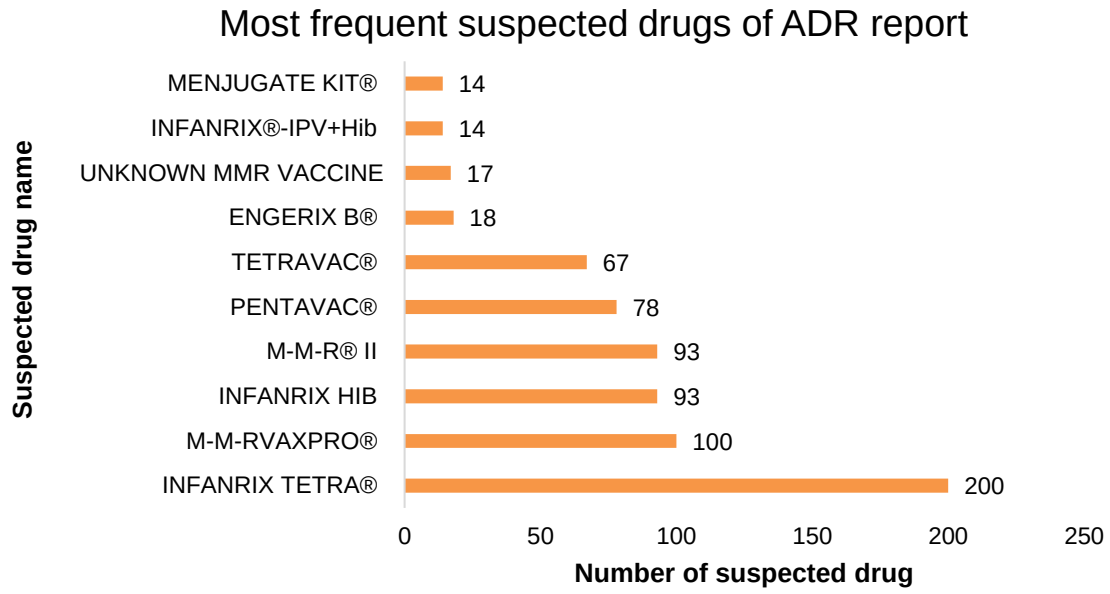

Figure 12. Most frequent suspected drugs of adverse drug reaction reported.

INFANRIX TETRA® Diphtheria, tetanus, pertussis and poliomyelitis vaccine
M-M-RVAXPRO® Measles, mumps and rubella vaccine
INFANRIX HIB Diphtheria, tetanus, pertussis and haemophilus type b vaccine
M-M-R® II Measles, mumps and rubella vaccine
PENTAVAC Diphtheria, tetanus, pertussis, poliomyelitis and haemophilus type b vaccine
TETRAVAC® Diphtheria, tetanus, pertussis and poliomyelitis vaccine
Engerix B® Hepatitis B vaccine
INFANRIX®-IPV+Hib Diphtheria, tetanus, pertussis, poliomyelitis and haemophilus type b vaccine
Menjugate Kit® Meningococcal vaccine

Table 4. ATC codes involved in suspected ADR per age group.

ATC Classification (N)	Age Group					Total N (%)
	[0-2m[N (%)	[2m-3y[N (%)	[3y-12y[N (%)	[12y-18y] N (%)	Unknown N (%)	
G02CB03 Cabergoline	1 (0,13%)	0 (0,00%)	0 (0,00%)	0 (0,00%)	0 (0,00%)	1 (0,13%)
J07A Bacterial Vaccines	0 (0,00%)	0 (0,00%)	1 (0,13%)	2 (0,26%)	0 (0,00%)	3 (0,39%)
J07AG Haemophilus influenzae B vaccines	0 (0,00%)	0 (0,00%)	0 (0,00%)	1 (0,13%)	0 (0,00%)	1 (0,13%)
J07AH Meningococcal vaccines	1 (0,13%)	12 (1,58%)	0 (0,00%)	1 (0,13%)	0 (0,00%)	14 (1,84%)
J07AH07 meningococcus C, purified polysaccharides antigen conjugated	0 (0,00%)	1 (0,13%)	0 (0,00%)	0 (0,00%)	0 (0,00%)	1 (0,13%)
J07AH09 meningococcus B, multicomponent vaccine	0 (0,00%)	1 (0,13%)	0 (0,00%)	1 (0,13%)	0 (0,00%)	2 (0,26%)
J07AL02 pneumococcus, purified polysaccharides antigen conjugated	2 (0,26%)	11 (1,45%)	1 (0,13%)	1 (0,13%)	0 (0,00%)	15 (1,97%)
J07AM51 tetanus toxoid, combinations with diphtheria toxoid	2 (0,26%)	1 (0,13%)	0 (0,00%)	1 (0,13%)	0 (0,00%)	4 (0,53%)
J07AX other bacterial vaccines	1 (0,13%)	**62 (8,15%)**	36 (4,73%)	1 (0,13%)	0 (0,00%)	100 (13,14%)
J07BC01 hepatitis B, purified antigen	1 (0,13%)	17 (2,23%)	1 (0,13%)	1 (0,13%)	0 (0,00%)	20 (2,63%)
J07BD52 measles, combinations with mumps and rubella, live attenuated	5 (0,66%)	34 (4,47%)	**75 (9,86%)**	**103 (13,53%)**	1 (0,13%)	218 (28,65%)
J07BD54 measles, combinations with mumps, rubella and varicella, live attenuated	0 (0,00%)	0 (0,00%)	0 (0,00%)	1 (0,13%)	0 (0,00%)	1 (0,13%)
J07BF03 poliomyelitis, trivalent, inactivated, whole virus	0 (0,00%)	1 (0,13%)	1 (0,13%)	1 (0,13%)	0 (0,00%)	3 (0,39%)
J07BH01 rota virus, live attenuated	0 (0,00%)	2 (0,26%)	0 (0,00%)	0 (0,00%)	0 (0,00%)	2 (0,26%)
J07BH02 rota virus, pentavalent, live, reasserted	0 (0,00%)	2 (0,26%)	1 (0,13%)	0 (0,00%)	0 (0,00%)	3 (0,39%)
J07BM01 papillomavirus (human types 6, 11, 16, 18)	0 (0,00%)	1 (0,13%)	0 (0,00%)	1 (0,13%)	0 (0,00%)	2 (0,26%)
J07CA02 diphtheria-pertussis-poliomyelitis-tetanus	0 (0,00%)	8 (1,05%)	**256 (33,64%)**	4 (0,53%)	2 (0,26%)	270 (35,48%)
J07CA05 diphtheria-hepatitis B-pertussis-tetanus	0 (0,00%)	0 (0,00%)	1 (0,13%)	0 (0,00%)	0 (0,00%)	1 (0,13%)
J07CA06 diphtheria-haemophilus influenzae B-pertussis-poliomyelitis-tetanus	**6 (0,79%)**	**53 (6,96%)**	39 (5,12%)	1 (0,13%)	0 (0,00%)	99 (13,01%)
N02BE01 paracetamol	0 (0,00%)	0 (0,00%)	1 (0,13%)	0 (0,00%)	0 (0,00%)	1 (0,13%)
Total N (%)	19 (2,50%)	206 (27,07%)	413 (54,27%)	120 (15,77%)	3 (0,39%)	761 (100%)

Table 5. Absolute and relative frequency of the suspected drugs of adverse drug reaction.

DRUG NAME	TOTAL (N)	TOTAL (%)
INFANRIX TETRA®	200	24,8
M-M-RVAXPRO®	100	12,5
INFANRIX HIB	93	11,6
M-M-R® II	93	11,6
PENTAVAC®	78	9
TETRAVAC®	67	8,3
ENGERIX B®	18	2
UNKNOWN MMR VACCINE	17	2,1
INFANRIX®-IPV+HIB	14	1,7
MENJUGATE KIT®	14	1,7
PREVENAR 13®	14	1,6
TRIVIRATEN BERNA	9	1,1
INFANRIX®	7	0,9
PENTAXIM®	6	0,6
ROTATEQ®	3	0,2
UNKNOWN DTAP-IPV VACCINE	3	0,4
BEXSERO®	2	0,1
BOOSTRIX®	2	0,2
DT VAX ADULTO®	2	0,2
DITANRIX®	2	0,2
GARDASIL®	2	0,2
POLIOVACCINE SSI	2	0,2
ROTARIX®	2	0,1
UNKNOWN HEPATITIS B VACCINE	2	0,2
DOSTINEX	1	0,1
IMOVAX® POLIO	1	0,1
INFANRIX PENTA®	1	0,1
MENINGITEC®	1	0,1
PANASORBE	1	0,1
PREVENAR®	1	0,1
TETRACT-HIB®	1	0,1
UNKNOWN DTPA VACCINE	1	0,1
UNKNOWN DTAP/IPV/HIB VACCINE	1	0,1
TOTAL N (%)	761	100

2.5. Discussion

In the present study, from 2012 to 2016 a total of 591 ADR reports, concerning paediatric individuals exposed to DTPa, and/ or to MMR vaccines, were analysed. These results are substantially lower when compared with ADR reporting in The Netherlands. In Portugal, the rate of ADR reports concerning this vaccines in 2015 was 4,5 reports per 100 000 paediatric individuals, in The Netherlands it was 28,9 reports per 100 000 paediatric individuals. According to Herdeiro et al., the main limitation of the Portuguese spontaneous drug notification system is ADR under-reporting, it is estimated that only 6% of the total adverse drug reaction are notified (40). The highest proportion of reported ADR occurred in 2013 (n=181), and the lowest proportion occurred in 2012 (n=86).

According to INFARMED records, the number of adverse drug reaction reports regarding all medicines, is slightly increasing over the years from 3104 reports in 2012 to 5698 reports in 2016, this result may be explained by the increasing awareness of reporters and pharmacovigilance system work progress over the years. Adverse reaction following immunization is decreasing over the years, this may be linked with the Portuguese paediatric population decrease over the same period. Vaccines (ATC: J07) represent 6% to 12% of the total ADR reported to INFARMED between 2012 to 2016, it is one of the most representative ATC codes nationally notified. Adverse drug reaction to DTPa and MMR vaccines in paediatrics occupies between 26,03% (2016) and 43,58% (2013) of the total reported ADR to vaccines (ATC: J07).

During this five-year period, the North region of Portugal has reported the highest number of adverse drug reaction, concerning all medicines, to the National Pharmacovigilance System. On the contrary, in this study, the highest proportion of ADR reports were notified by the Centre region (n=215) and the North region occupies the third place (n=132).

The highest number of ADR, related to these vaccines were directly reported by nurses, if we compare this data to the overall ADR reports received by the INFARMED in the same period, we can realise that the highest frequency of ADR notification was done by the physician, followed by the pharmacist, and nurse occupies the third place in ADR reporting. The important role of nurse in reporting suspected ADRs in paediatrics has been verified in other studies. Hawcutt et al. conducted a study in the UK and concluded that nurse reports more suspected ADRs in children than any other health professional (74). This findings, however differ from The Netherlands case, where the patient is the first ADR reporter, followed by physician, pharmacist and general practitioners (75). In a study conducted in the Netherlands, the main reasons for patient to report ADR were to share their experiences, the severity of the reaction, worries about their own situation and the fact the ADR was not mentioned in the patient information leaflet (76).

Nurses are the healthcare professional responsible by vaccine administration in healthcare institutions, this may explain their important role in the process of AEFI spontaneous reporting in paediatrics.

The age group affected more prevalent among DTPa and MMR ADR reports was from 3 years (inclusive) to 12 years (exclusive), a male predominance was found. This findings are in accordance with other AEFI studies concerning paediatric population (77).

The system organ class most frequently involved in ADR reports was general disorders and administration site conditions. Pyrexia and vaccination site reactions such as oedema, erythema, warmth and pain were the most frequently reported adverse reactions. These results are in accordance with other studies. In a study conducted by Lareb, in 2015 in The Netherlands the most cited adverse event following immunisation was injection site reaction

(78), a study conducted in Denmark reported pyrexia and injection-site reactions as the most frequently reported AEFI following paediatric immunization (79), another study in Czech Republic reported local (redness, swelling, pain) as the most frequent AEFI (77).

The system organ class injury, poisoning and procedural complications was the second most significant in terms of ADR reporting, since in the field of immunization, vaccine failure and lack of efficacy is considered an adverse drug reaction.

From the total ADR reported in this study, 55,33% adverse reactions were considered serious. According to INFARMED data on ADR concerning all medicines in Portugal, between 2012 and 2016 a total of 19952 ADR was reported, from those 14850 (74,43%) reports were classified as serious. These results may be linked to the special awareness of the pharmaceutical industry and healthcare professionals to report serious events in Portugal. In the older age group (12 years old to 18 years old), only serious adverse drug reaction was reported.

The most frequent drugs suspected of ADR report in this study were INFARIX TETRA® against diphtheria, tetanus, pertussis and poliomyelitis and M-M-RVAXPRO® against measles, mumps and rubella. In march 2014, the batch number AC20B268AB of INFARIX TETRA® was suspended due to AEFI notifications reporting limb cellulitis, redness and fever (80).

It is important to note that, in this study, other drugs than vaccines were classified as suspected drugs of causing the adverse drug reaction (as for example: Panasorbe®). This happens when more than one drug or vaccines are administered to the same subject in a similar temporal window, and we cannot exclude any of these medicines as suspected drug of adverse reaction without an appropriate causality assessment.

In this study, 71,06% of patients that reported an ADR completely recovered, still a vast percentage of the study population (20,13%) ADR outcome is unknown, in some cases healthcare professionals are unable to follow patient case evolution.

2.5.1. Limitations

The main limitation of this study is the absence of causality assessment of adverse drug reaction to the suspected vaccine, which we did not get assess to. This study may be susceptible to population selection bias, since in Portugal reports of serious ADR are specially encouraged.

ADR under-reporting constitutes a limitation to this study, the spontaneous reports received illustrates just part of a wider reality.

3. CHAPTER 3 – ANALYSIS OF VACCINE COVERAGE AND VACCINE PREVENTABLE DISEASE CASES IN PORTUGAL AND IN THE NETHERLANDS

3.1. Introduction

The Portuguese National Immunization Program is available to every citizen present in Portugal, including legal and illegal immigrants (35). There are different vaccination schemes according to individual age, vaccine status, risk groups and other special circumstances (35). The recommended vaccine schedule objective is to achieve the best protection in the most adequate age and earlier as possible, because it is in the first year of age that children are most vulnerable to infectious diseases (35). Immunization should be scrupulously fulfilled at the recommended age without any delay to avoid disease complications which can be fatal (35).

The immunisation coverage for the different vaccination included in the Netherlands' NIP was with 92% to 99% high in report year 2016 (38). However, participation for most vaccinations declined by about 0,5% (38). For new-borns, this decline was observed for the second consecutive year (38). Such fluctuations were observed previously at regional level, but they are now, for the first time being observed nationwide (38).

This raises a huge concern over the future of NIP, if vaccine coverage continues to decrease we will not be able to maintain herd immunity and consequently population will be susceptible to vaccine-preventable diseases.

3.2. Aims

The outcome of this study is to analyse vaccine coverage variation and the number of vaccine-preventable disease cases in paediatrics in Portugal and in The Netherlands, where anti-vaccination movements are well-known.

3.3. Methods

3.3.1. Data Sources

For this study, NIP vaccine coverage data was collected from 2012 to 2016. Vaccine coverage was assessed at the age of 2 years old. So, we analysed vaccine coverage per vaccine, for age cohorts of newborns from 2010 to 2014.

Portuguese vaccine coverage data was extracted from 2012 to 2016 for cohorts 2010 to 2014 from the temporal series results of the evaluation of NIP, available on Directorate-General of Health (DGS) website (81). MMR vaccine data from 2012 for cohort 2010 was

extracted from vaccination bulletin n.er 6, available on DGS website, data from 2013 for cohort 2011 was extracted from vaccination bulletin n.er 7, available on DGS website, data from 2014 to 2016 for cohorts 2012 to 2014 was extracted from the temporal series results of the evaluation of NIP, available on DGS website (81–83).

Vaccine coverage data from The Netherlands NIP, from 2012 to 2016 for cohorts 2010 to 2014 was extracted from Netherlands' National Vaccination Programme 2016 report (84).

Vaccine preventable disease cases, for diseases included in the NIP, were analysed for Portugal and The Netherlands, from 2010 to 2016, in some cases data was not available for this period. Data was extracted from Surveillance Atlas of Infectious Diseases available on the European Centre for Disease Prevention and Control (ECDC) website.

3.3.2. Variables

The variables analysed were vaccine coverage percentage (%) per vaccine included in the NIP, per age cohort of newborns (2 years old).

Vaccine preventable disease cases were analysed. We studied the reported number of cases per vaccine preventable disease included in the NIP per year, notification rate (number of cases per 100 000 population), age group (percentage of childhood cases, from birth to 14 years old) and gender of the notified case, when available, we also included the number of deaths caused by the disease.

3.3.3. Analysis

A descriptive analysis was preformed to compare vaccine coverage data from Portugal to The Netherlands, we constructed bar graphs to analyse data.

Narrative analysis was used as well, to examine vaccine preventable disease cases data extracted from Portugal and from The Netherlands.

3.4. Results

3.4.1. Vaccine coverage evolution in Portugal and in The Netherlands

Vaccine coverage data was analysed for age cohorts of newborns (2 years old) 2010 to 2014 corresponding to the reporting year 2012 to 2016. Figure 24, represents the percentage of individuals, per age cohort per vaccine, who fulfilled for each vaccine the recommended vaccination plan, for Portugal and for the Netherlands (81–84).

In Portugal, the immunisation coverage (participation) on vaccines included in the NIP is considered a case of success with 96,1% to 99,1%, it is above WHO recommendations of 95% vaccination coverage. Vaccine coverage analysis shows slight variations over the selected age

cohorts. DTPa vaccine coverage suffered minor variations over the years, although, it continuously assured a minimum 96% vaccine coverage, in cohort 2010, vaccine coverage was 96,4% and in cohort 2014 it was 96,1% (figure 14). MMR vaccine coverage slightly changed from 98,0% to 97,9% (figure 15). Hib vaccine coverage increased from 96,3% in cohort 2010 to 98,7% in cohort 2014 (figure 16). BCG vaccine coverage ranges from 98,9% to 97,5% (figure 13), HBV from 98,5% to 98,3% (figure 18) and MenC from 98,5% to 97,3% (figure 17).

In the Netherlands vaccine coverage is considered high although in some cohorts it does not match with the 95% vaccine coverage recommendations of WHO. HBV vaccine coverage has increased over the studied cohorts with 19,7% for cohort 2010 to 93,1% for cohort 2014, although it does not comply with the 95% coverage, it suffered a great increase over the cohorts. In contrast, for the other vaccines we are experiencing vaccine coverage decline over the age cohorts, DTPa with 95,5% to 93,5% (figure 14), MMR with 96,1% to 93,8% (figure 15), Hib with 96,1% to 94,2% (figure 16) and MenC with 96,0% to 93,5% (figure 17).

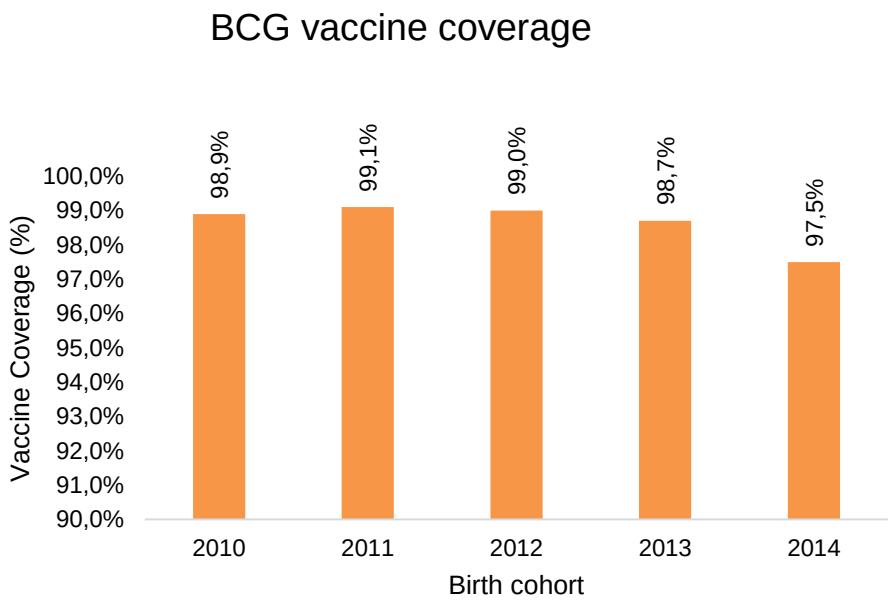

Figure 13. Vaccine coverage for birth cohorts of newborns (2 years old) 2010 to 2013, for Bacillus Calmette-Guérin (BCG) vaccine in Portugal (81).

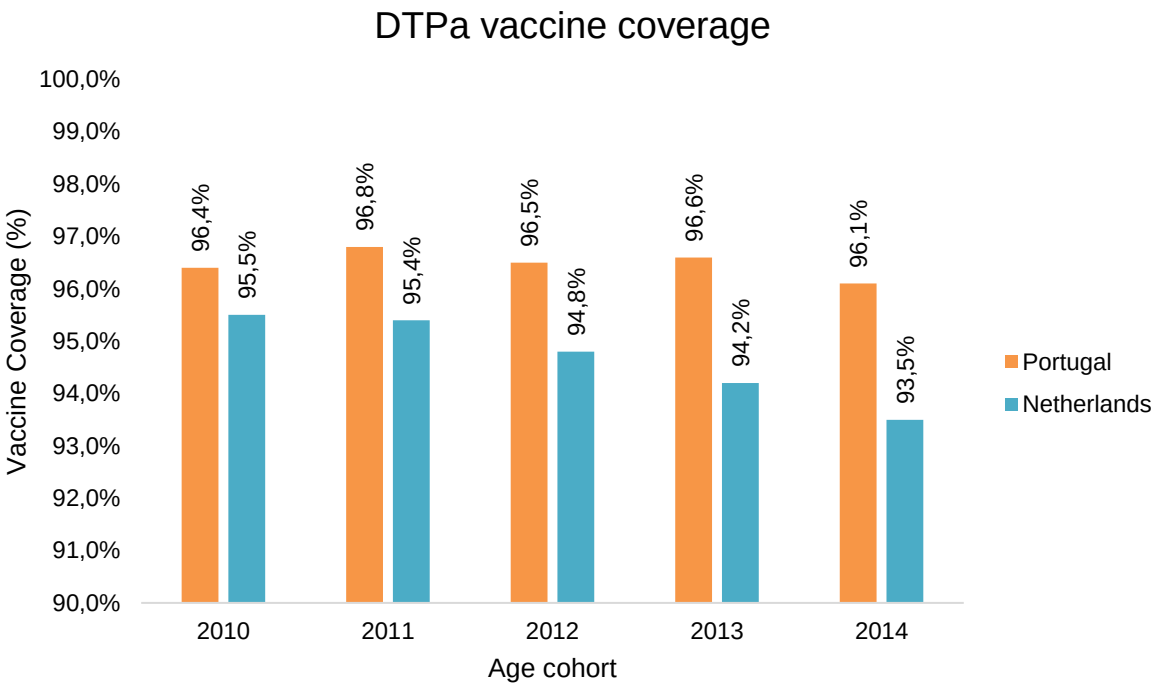

Figure 14. Diphtheria, tetanus and acellular pertussis (DTPa) vaccine coverage for birth cohorts of newborns (2 years old) from 2010 to 2013 in Portugal and in the Netherlands (81,84).

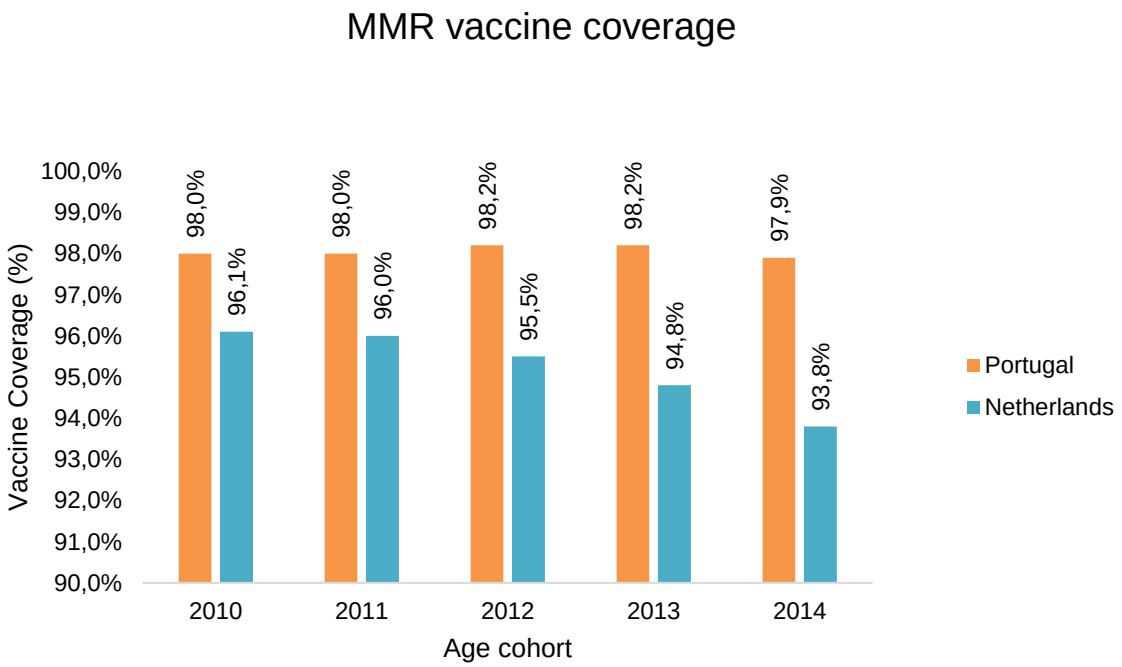

Figure 15. Measles, mumps and rubella (MMR) vaccine coverage for birth cohorts of newborns (2 years old) from 2010 to 2013 in Portugal and in the Netherlands (81–84).

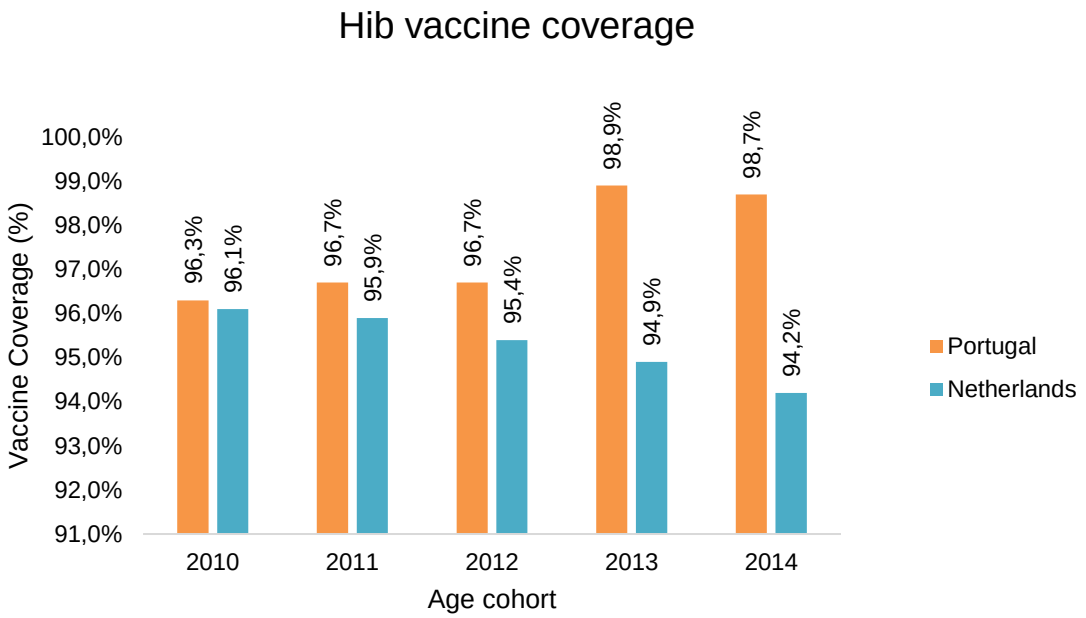

Figure 16. Haemophilus Influenzae type b (Hib) vaccine coverage for birth cohorts of newborns (2 years old) from 2010 to 2013 in Portugal and in the Netherlands (81,84).

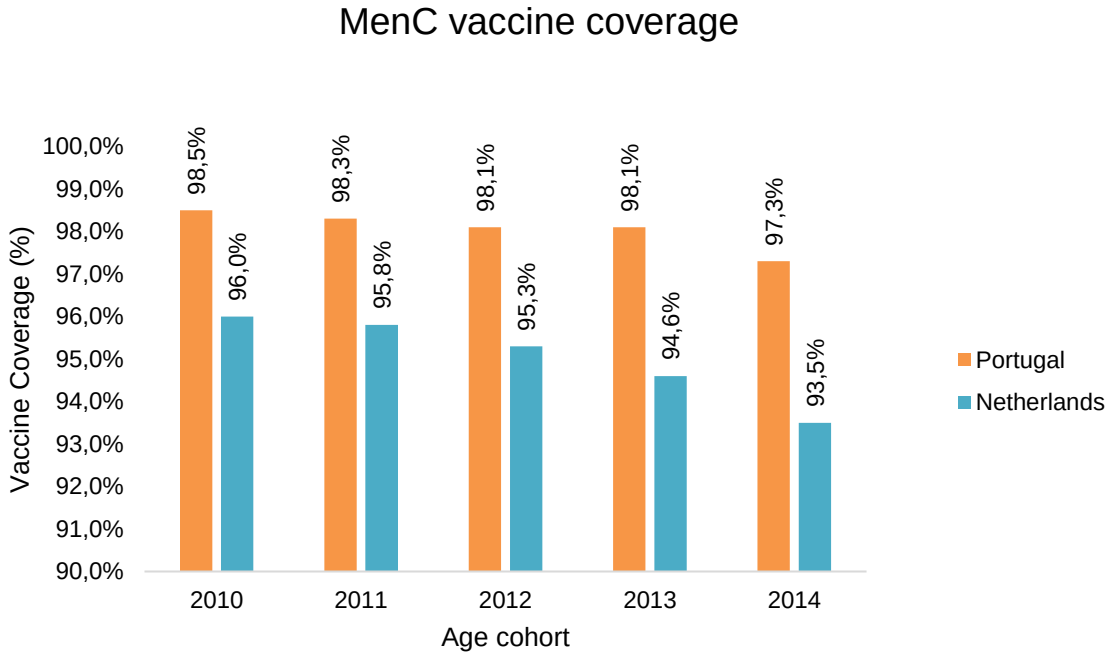

Figure 17. meningococcal C (MenC) vaccine coverage for birth cohorts of newborns (2 years old) from 2010 to 2013 in Portugal and in the Netherlands (81,84).

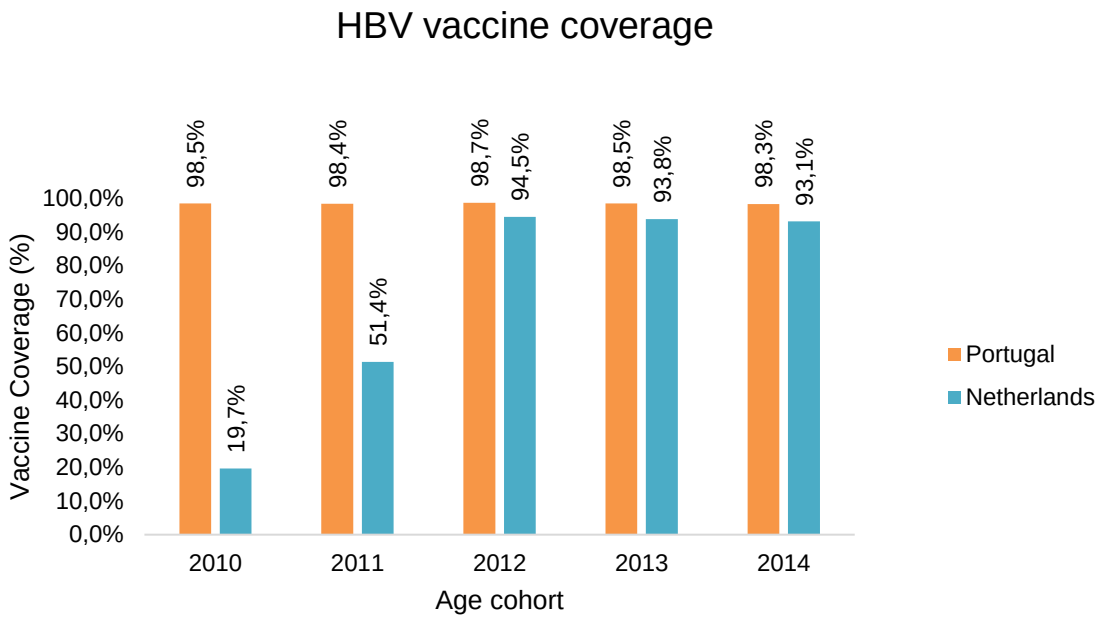

Figure 18. Hepatitis B (HBV) vaccine coverage for birth cohorts of newborns (2 years old) from 2010 to 2013 in Portugal and in the Netherlands (81,84).

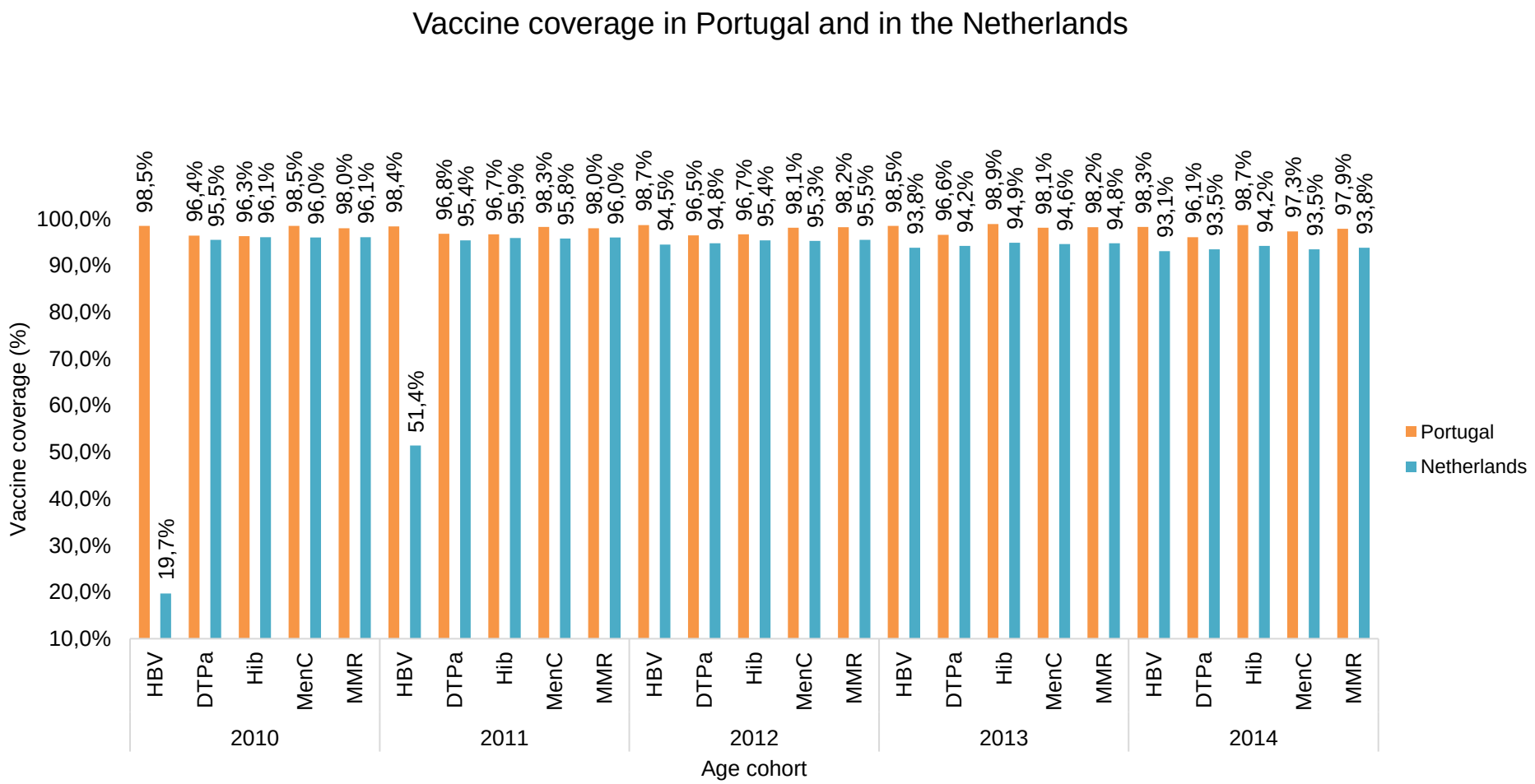

Figure 19. Vaccine coverage for birth cohorts of newborns (2 years old) 2010 to 2013 in Portugal and in The Netherlands regarding NIP vaccines against Hepatitis B (HBV), Diphtheria, tetanus and acellular pertussis (DTPa), Haemophilus Influenzae type b (Hib), meningococcal C (MenC), Measles, mumps and rubella (MMR) (81–84).

3.4.2. Vaccine preventable disease cases analysis

Vaccine preventable disease reported number cases and notification rate per 100 000 population were analysed in Portugal and in the Netherlands for the period 2010 to 2016 (measles and rubella). In case of hepatitis B and diphtheria, the period available for consultation was from 2010 to 2014. For tetanus, pertussis, invasive H. influenzae serotype B, mumps and tuberculosis it was possible to extract information from 2010 to 2015 (table 6). Data was extracted from ECDC Surveillance Atlas of Infectious Diseases. Note that we are analysing the number of reported cases, since we lack disease case confirmation, the number of reported cases can be higher than the real number of disease cases.

In Portugal, the overall notification rate of vaccine preventable disease reported cases is considered low when compared with the European notification rate.

3.4.2.1. Hepatitis B

The number of hepatitis B reported cases in Portugal suffered a slight increase from 0 cases in 2010 to 19 cases in 2014, which represents a notification rate increase from 0 to 0,18 cases per 100 000 population. From 2010 to 2014, 34 cases of hepatitis B were reported, only 1 case occurred in paediatric age (0-4 years), 69% cases occurred in male gender and 31% cases in female gender (figure 20). Although in the Netherlands the number of hepatitis B reported cases are decreasing, the numbers are still very high when compared to Portugal, ranging from 196 reported cases in 2010 to 142 in 2014 (1,18/ 100 000 population in 2010 to 0,84/ 100 000 in 2014). From the total of 813 hepatitis B reported cases, 9 cases occurred in paediatric age (1 case – 0-4 years; 8 cases – 5-14 years), 77% cases occurred in male, 23% cases in female (table 6).

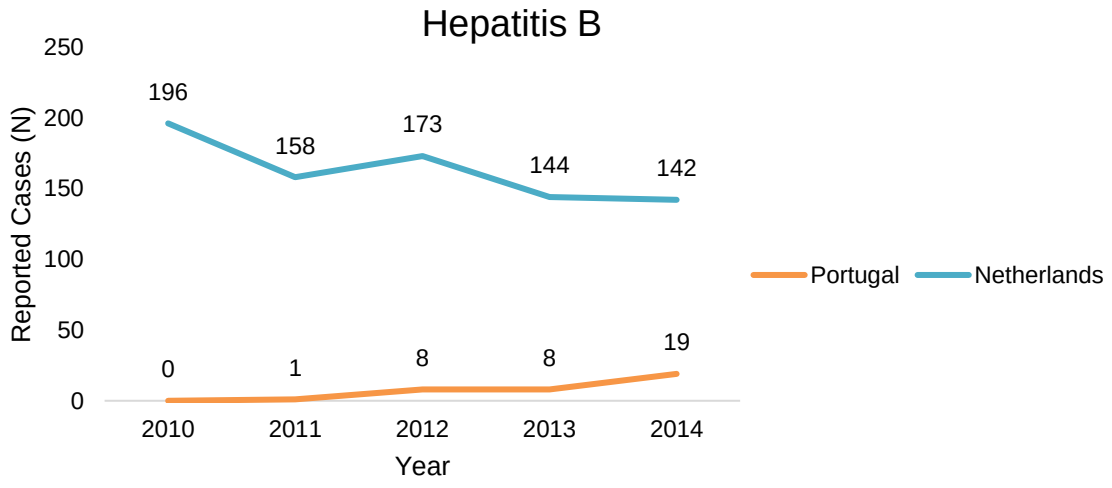

Figure 20. Hepatitis B reported number cases per year from 2010 to 2014 in Portugal and in the Netherlands.

3.4.2.2. Tetanus

Tetanus reported number cases in Portugal has maintained very low levels, resulting in small variations over the analysed period of time, with 3 reported cases in 2010 to 1 reported cases in 2015 (0,03/ 100 000 population in 2010 to 0,01/ 100 000 in 2015). During this 5 years, 10 cases of tetanus were reported, resulting in 2 deaths, none of the reported cases occurred in paediatric age, and 20,00% reported cases occurred in male, 80,00% in female (figure 21). In the Netherlands notification rate is close to the Portuguese, although in 2011 there were 6 reported cases (0,04/ 100 000 population), in 2010 and in 2015 only one case of tetanus was reported (0,01/ 100 000 in 2010 and in 2015). From 2010 to 2015 there were 11 cases of tetanus, resulting in one death in 2011, none of the reported cases occurred in paediatric age, and 73,00% cases occurred in male, 27,00% in female (table 6).

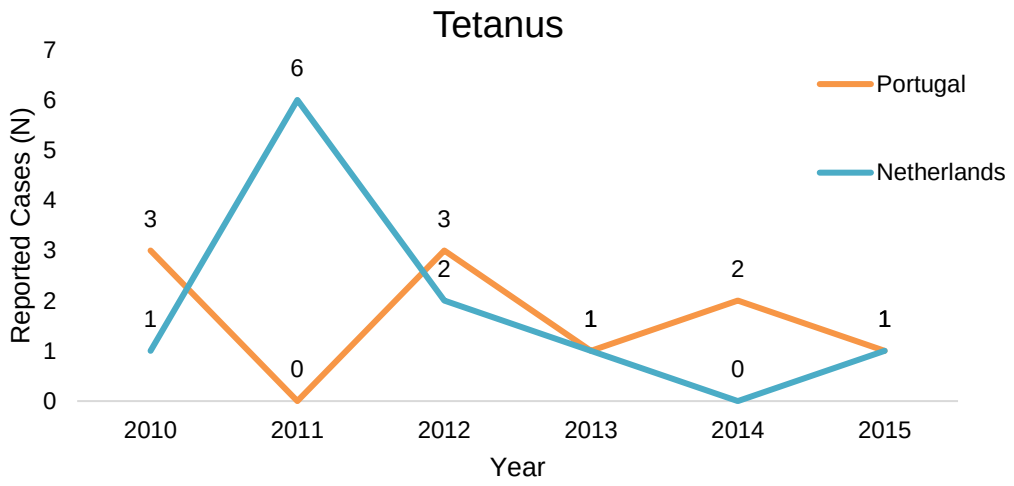

Figure 21. Tetanus reported number cases per year from 2010 to 2015 in Portugal and in the Netherlands.

3.4.2.3. Pertussis

A notable increase in the notification rate of pertussis was observed in Portugal, 14 reported cases in 2010 to 238 reported cases in 2015 (0,13/ 100 000 population in 2010 to 2,29/ 100 000 in 2015). From 2010 to 2015 there were 701 reported cases of pertussis, resulting in a total of 8 deaths, 649 notified cases occurred in paediatric age (604 cases – 0-4 years, 45 cases – 5-14 years), 48% cases occurred in male, 52% cases were from female. The Netherlands suffered an outstanding increase in the notification rate of pertussis from 22,52 cases per 100 000 population in 2010 (3733 reported number cases) to 36,55 cases per 100 000 population in 2015 (6178 reported number cases) with a total of 39260 reported cases from 2010 to 2015, which resulted in 6 deaths. 14229 cases occurred in paediatric age (2192

cases – 0-4 years, 12037 cases – 5-14 years), 44% of cases occurred in male, 56% cases in female (figure 22).

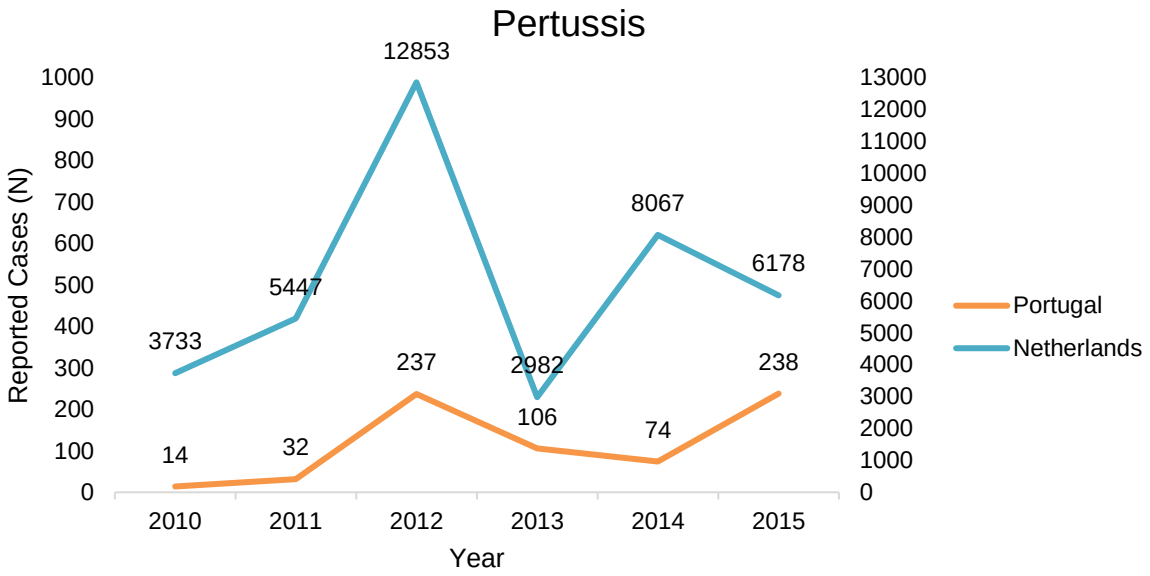

Figure 22. Pertussis reported number cases per year from 2010 to 2015 in Portugal and in the Netherlands. Primary axis: Portugal's reported cases number; secondary axis: The Netherlands' reported cases number.

3.4.2.4. Invasive *Haemophilus influenzae* serotype B

The number of reported cases of invasive *Haemophilus influenzae* serotype B has maintained low levels in Portugal, with 5 reported cases in 2011 to 2 reported cases in 2015. During the same period, the total number of reports was 22, causing 3 deaths. From the total reported cases 11 occurred in paediatric age (6 cases – 0-4 years, 5 cases – 5-14 years), 68% of cases occurred in male, 32% cases in female. In the Netherlands reported number cases are higher than in Portugal, with 37 reported cases in 2010 to 34 reported cases in 2015. Although the number of reported cases are decreasing over the years, it is still a case of concern. From 2010 to 2015 178 cases of disease were reported, 65 reported cases occurred in paediatric age (55 cases – 0-4 years, 10 cases – 5-14 years), 49% of cases occurred in male, 51% cases in female (figure 23).

3.4.2.5. Invasive meningococcal disease serotype C

In Portugal as it happens in the Netherlands reported number cases of invasive meningococcal disease serotype C assume very low levels, notification rate per 100 000 population in Portugal was 0.06 in 2010 and 0.04 in 2015, in the Netherlands notification rate was 0.06 in 2010 and 0.05 in 2015. In Portugal, from 2010 to 2015 there were 20 reported cases of disease, 4 cases occurred in paediatric age (1 case – 0-4 years, 3 cases – 5-14 years), 27% of reports occurred in male, 73% in female. In the Netherlands, during this period

a total of 34 cases were reported, 8 cases occurred in paediatric age (0-4 years), 56% cases occurred in male, 44% cases occurred in female (figure 24).

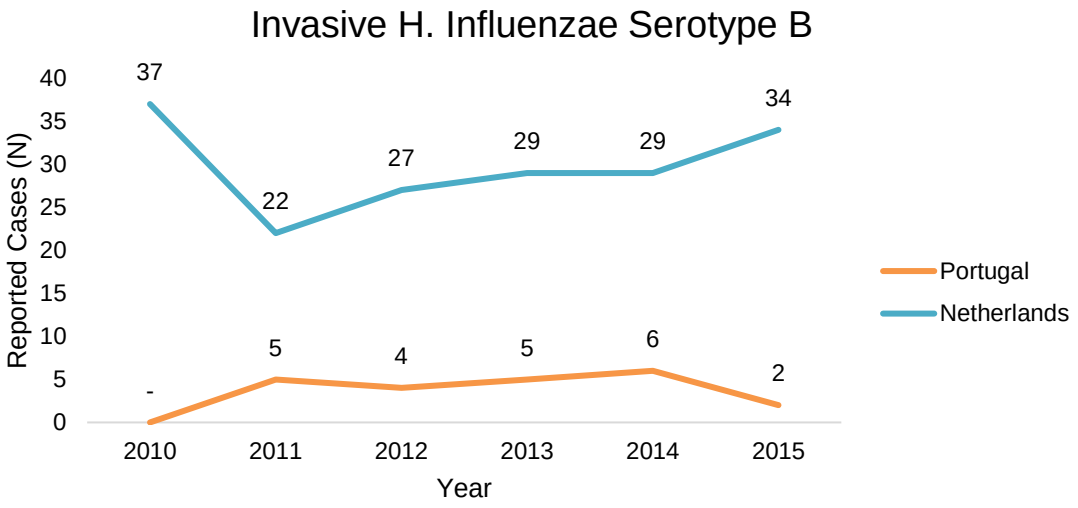

Figure 23. Invasive Haemophilus influenzae serotype B reported number cases per year from 2011 to 2015 in Portugal and from 2010 to 2015 in the Netherlands. Reported number cases in 2010 for Portugal were not available.

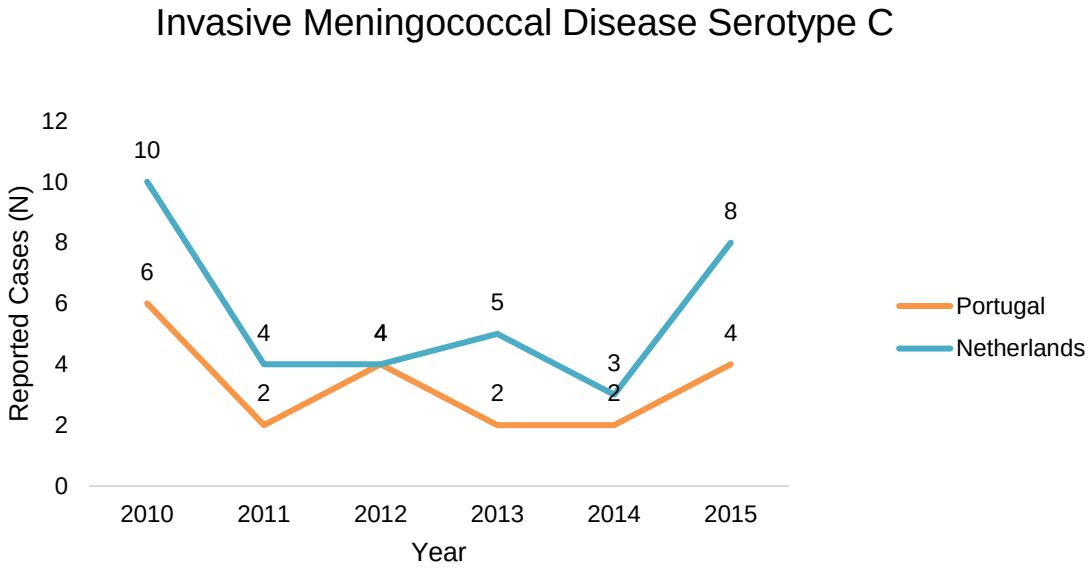

Figure 24. Invasive Meningococcal disease serotype C reported number cases per year from 2010 to 2015 in Portugal and in the Netherlands.

3.4.2.6. Measles

The number of reported cases of Measles is decreasing over the years in Portugal, with 5 reported cases in 2010 to 0 reported cases in 2016 (0,47/ 100 000 population in 2010), from 2010 to 2016 a total of 15 cases were reported, 4 cases occurred in paediatric age (0-4 years),

47% cases occurred in male, 53% cases in female. In the Netherlands, although reported cases are decreasing over the years, 2010 with 15 reported cases and 2016 with 6 reported cases (0,9/ 100 000 in 2010 and 0,36/ 100 000 in 2016), there was a peak of reported cases in 2013 with 2872 reported number cases of Measles (157,33/ 100 000). From 2010 to 2016 a total of 2872 cases were reported, resulting in one death. 2240 reported cases occurred in paediatric age (527 cases – 0-4 years, 1713 cases – 5-14 years), 50% cases occurred in male, 50% cases in female (figure 25).

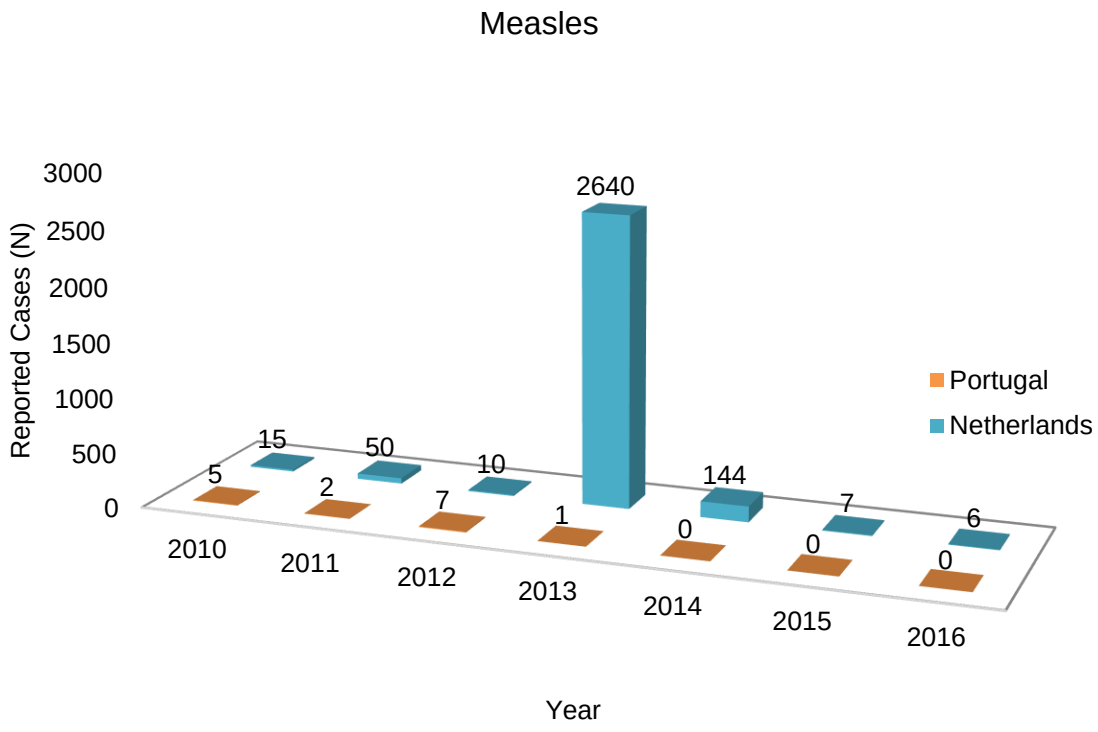

Figure 25. Measles reported number cases per year from 2010 to 2016 in Portugal and in the Netherlands.

3.4.2.7. Mumps

In Portugal, the number of reported cases of mumps suffered slight variations over the years maintaining almost the same levels, from 140 reported cases of measles in 2010 to 146 cases in 2015 (1,32/ 100 000 population in 2010 to 1,41/ 100 000 in 2015). From a total of 821 during this five years, 584 cases occurred in paediatric age (248 cases – 0-4 years, 336 cases – 5-14 years), 59% cases occurred in male, 41% cases in female. In the Netherlands notification rate per 100 000 population is decreasing over the years, but numbers are still very high when compared to Portugal, with 424 reported cases in 2010 to 87 reported cases in 2015 (2,56/ 100 000 in 2010 to 0,51/ 100 000 in 2015). A total of 1800 cases were reported between

2010 and 2015, 100 cases occurred in paediatric age (20 cases – 0-4 years, 80 cases – 5-14 years), 58% cases occurred in male, 42% cases in female (figure 26).

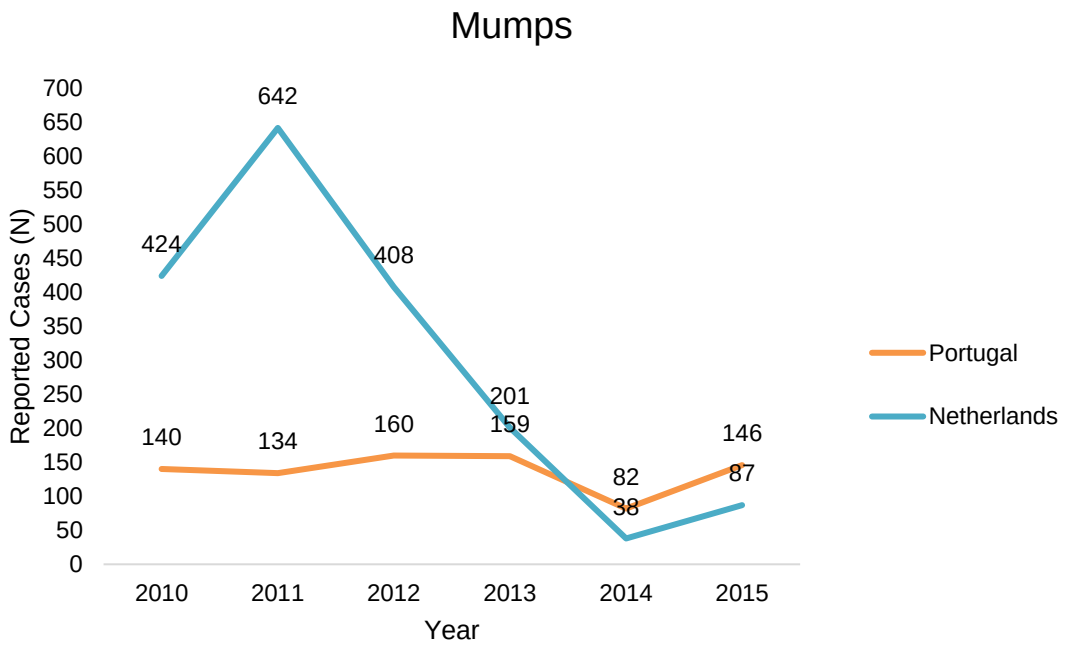

Figure 26. Mumps reported number cases per year from 2010 to 2015 in Portugal and in the Netherlands.

3.4.2.8. Rubella

Rubella number of reported cases has slightly increased over the years in Portugal, with 1 report in 2010 to 8 reports in 2016 (0,09/ 100 000 population in 2010 to 0,77/ 100 000 in 2016). A total of 24 cases were reported between 2010 and 2016, 20 cases occurred in paediatric age (15 cases – 0-4 years, 5 cases – 5-14 years), 38% cases occurred in male, 63% cases in female. In the Netherlands reported cases are very low, although in 2013 57 cases of rubella were reported (3,40/ 100 000). A total of 62 cases were reported between 2010 and 2016, 53 cases occurred in paediatric age (11 cases – 0-4 years, 42 cases – 5-14 years), 57% cases occurred in male, 43% cases in female (figure 27).

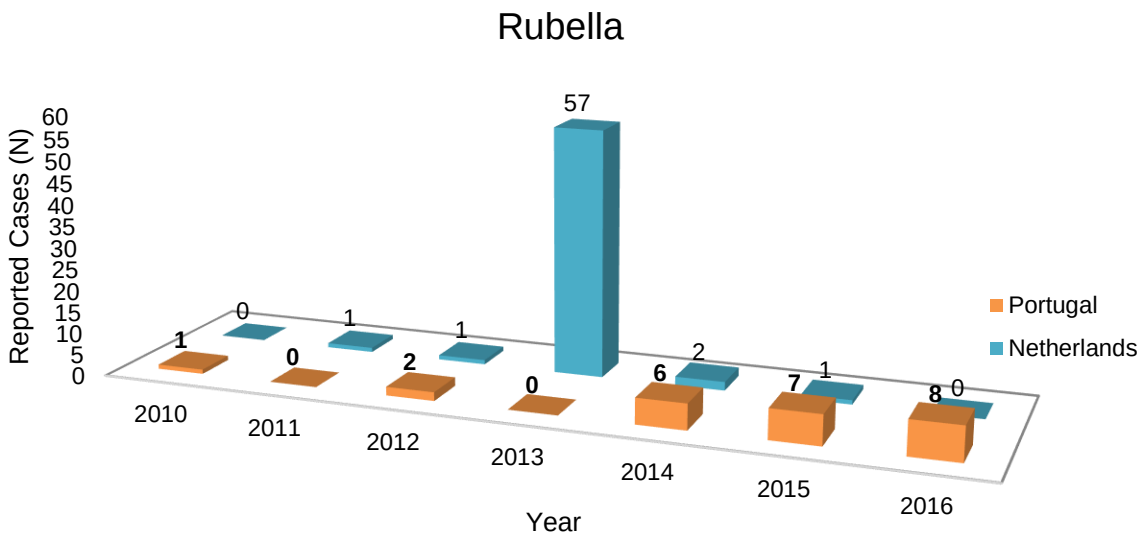

Figure 27. Rubella reported number cases per year from 2010 to 2015 in Portugal and in the Netherlands.

3.4.2.9. Diphtheria

In Portugal from 2010 to 2014 we did not have any reported case of diphtheria. In the Netherlands, we had one case of diphtheria in 2012 and another in 2014 (figure 28).

3.4.2.10. Tuberculosis

Tuberculosis notification rate is high in Portugal, ranging from 2715 reported cases in 2010 to 2124 reported cases in 2015 (25,68/ 100 000 population in 2010 to 20,47/ 100 000 in 2015). A total of 14742 cases of tuberculosis were reported between 2010 and 2015, 9879 cases occurred in paediatric age (186 cases – 0-4 years, 9693 cases – 5-14 years), 66% reported cases occurred in male, 34% cases in female. In the Netherlands, notification rate is considerably lower than in Portugal, with 1068 reported cases in 2010 to 867 reported cases in 2015 (6,44/ 100 000 in 2010 to 5,13/ 100 000 in 2015). A total of 5554 cases were reported between 2010 and 2015, 263 cases occurred in paediatric age (78 cases – 0-4 years, 185 cases – 5-14 years), 58% reported cases occurred in male, 42% cases in female (figure 29).

In table 6, we present the reported cases and notification rate per 100 000 population, of selected vaccine preventable diseases, with information about age and gender of the individual, in Portugal and in the Netherlands by year.

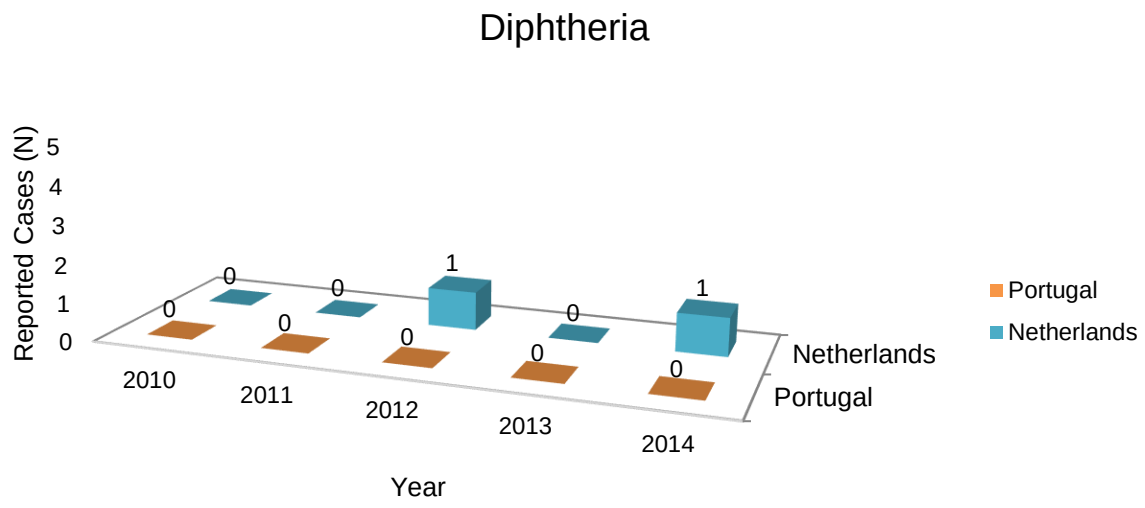

Figure 28. Diphtheria reported number cases per year from 2010 to 2015 in Portugal and in the Netherlands.

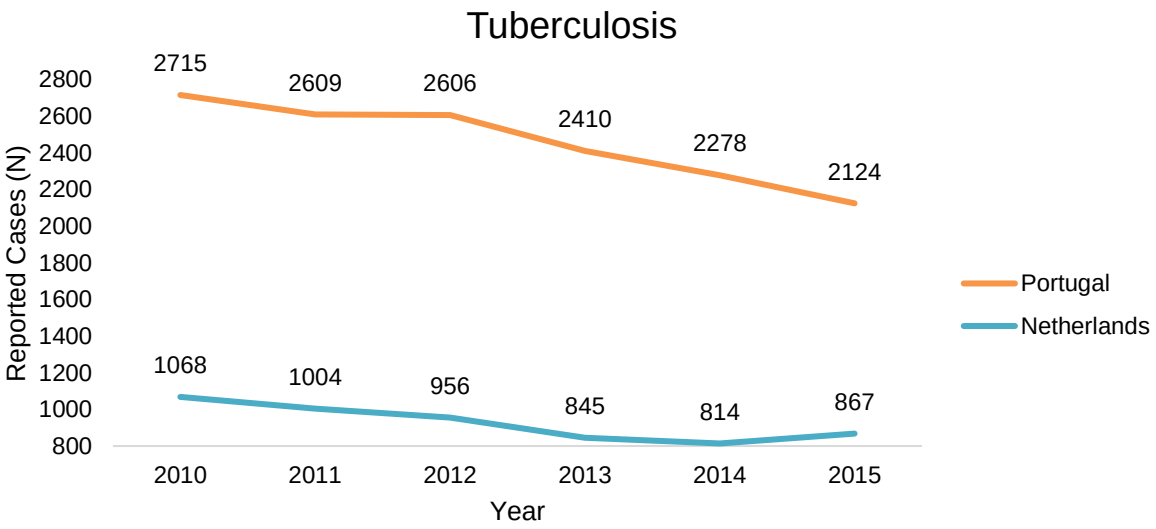

Figure 29. Tuberculosis reported number cases per year from 2010 to 2015 in Portugal and in the Netherlands.

Table 6. Reported cases and notification rate of selected vaccine preventable diseases with information about age and gender, in Portugal and in the Netherlands by year.

Disease	Year	Portugal							Netherlands						
		Reported cases (N)	Notification rate (N/100000)	Number of deaths (N)	Age (%)		Gender (%)		Reported cases (N)	Notification rate (N/100000)	Number of deaths (N)	Age (%)		Gender (%)	
					0-4y	5-14y	Male	Female				0-4y	5-14y	Male	Female
Hepatitis B	2010	0	0	n.d.	0	0	0	0	196	1,18	n.d.	0	0,5	79,1	20,9
	2011	1	0,01	n.d.	0	0	100	0	158	0,95	n.d.	0	0,6	77,8	22,2
	2012	8	0,08	n.d.	0	0	75	25	173	1,03	n.d.	0,6	1,7	79,2	20,8
	2013	8	0,08	n.d.	12,5	0	87,5	12,5	144	0,86	n.d.	0	1,4	74,3	25,7
	2014	19	0,18	n.d.	0	0	57,9	42,1	142	0,84	n.d.	0	0,7	74,6	25,4
Tetanus	2010	3	0,03	0	0	0	0	100	1	0,01	0	0	0	0	100
	2011	0	0	0	0	0	0	0	6	0,04	1	0	0	66,7	33,3
	2012	3	0,03	1	0	0	33,3	66,7	2	0,01	0	0	0	100	0
	2013	1	0,01	0	0	0	100	0	1	0,01	0	0	0	100	0
	2014	2	0,02	1	0	0	0	100	0	0	0	0	0	0	0
	2015	1	0,01	0	0	0	0	100	1	0,01	0	0	0	100	0
Pertussis	2010	14	0,13	0	100	0	57,1	42,9	3733	22,52	0	6,8	30,7	46,5	53,5
	2011	32	0,3	0	96,9	0	43,8	56,3	5447	32,7	3	5,8	35,1	46	54
	2012	237	2,25	4	91,6	4,3	46	54	12853	76,82	2	4,1	29,6	44,5	55,5
	2013	106	1,01	2	81,1	7,5	42,5	57,5	2982	17,77	1	5,7	26	44,9	55,1
	2014	74	0,71	0	91,9	2,8	47,3	52,7	8067	47,93	0	7,1	31,1	43,6	56,4
	2015	238	2,29	2	79	10,5	52,9	47,1	6178	36,55	0	5,7	30,6	41,9	58,1
Invasive *Haemophilus influenzae* serotype B	2010	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	37	0,22	n.d.	24,3	0	45,9	54,1
	2011	5	0,05	0	40	0	80	20	22	0,13	n.d.	27,2	4,5	31,8	68,2
	2012	4	0,04	0	25	0	100	0	27	0,16	n.d.	22,2	14,8	55,6	44,4
	2013	5	0,05	0	20	40	80	20	29	0,17	n.d.	44,8	3,4	35,7	64,3
	2014	6	0,06	2	16,7	33,3	50	50	29	0,17	n.d.	27,5	10,3	53,6	46,4

	2015	2	n.d.	1	50	50	0	100	34	0,2	0	38,2	2,9	64,7	35,3
Invasive meningococcal disease serotype C	2010	6	0,06	n.d.	0	33,3	40	60	10	0,06	n.d.	30	0	50	50
	2011	2	0,02	n.d.	0	50	50	50	4	0,02	n.d.	0	0	25	75
	2012	4	0,04	n.d.	0	0	25	75	4	0,02	n.d.	75	0	75	25
	2013	2	0,02	n.d.	0	0	0	100	5	0,03	n.d.	0	0	60	40
	2014	2	0,02	n.d.	50	0	0	100	3	0,02	n.d.	0	0	33,3	66,7
	2015	4	0,04	n.d.	0	0	25	75	8	0,05	n.d.	25	0	75	25
Measles	2010	5	0,47	0	0	0	60	40	15	0,9	0	20	13,3	60	40
	2011	2	0,19	0	50	0	100	0	50	3	0	8	26	52	48
	2012	7	0,66	0	42,9	0	28,6	71,4	10	0,6	0	30	0	50	50
	2013	1	0,1	0	0	0	0	100	2640	157,33	1	17,8	63,6	49,2	50,8
	2014	0	0	0	0	0	0	0	144	8,56	0	32,7	11,8	60,8	39,2
	2015	0	0	0	0	0	0	0	7	0,41	0	0	0	85,7	14,3
	2016	0	0	0	0	0	0	0	6	0,36	0	0	33,3	33,3	66,7
Mumps	2010	140	1,32	n.d.	33,5	41,4	60,7	39,3	424	2,56	n.d.	1,9	4,1	57,6	42,4
	2011	134	1,27	n.d.	34,3	41,1	57,5	42,5	642	3,85	n.d.	0,9	5	60,9	39,1
	2012	160	1,52	n.d.	23,1	36,9	57,5	42,5	408	2,44	n.d.	0,7	4,9	57,1	42,9
	2013	159	1,52	n.d.	23,9	46,5	59,1	40,9	201	1,2	n.d.	1,5	1,5	58,2	41,8
	2014	82	0,79	n.d.	42,7	31,7	61	39	38	0,23	n.d.	0	10,5	50	50
	2015	146	1,41	n.d.	30,8	43,8	58,2	41,8	87	0,51	n.d.	0	4,6	52,9	47,1
Rubella	2010	1	0,09	0	0	0	0	0	0	0	0	0	0	0	0
	2011	0	0	0	0	0	0	0	1	0,06	0	0	0	0	0
	2012	2	0,19	0	0	0	0	0	1	0,06	0	0	0	0	100
	2013	0	0	0	0	0	0	0	57	3,4	0	17,5	73,7	55	45
	2014	6	0,58	0	n.d.	n.d.	n.d.	n.d.	2	0,12	0	50	0	100	0
	2015	7	0,67	0	100	0	n.d.	n.d.	1	0,06	0	0	0	100	0
	2016	8	0,77	0	0	0	0	0	0	0	0	0	0	0	0
Diphtheria	2010	0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
	2011	0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
	2012	0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	1	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.

	2013	0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
	2014	0	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	1	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Tuberculosis	2010	2715	25,68	n.d.		0,7	1,5	67	33	1068	6,44	n.d.		1	2,2	56	44
	2011	2609	24,68	n.d.		0,9	1	67,5	32,5	1004	6,03	n.d.		1,7	3,9	56,5	43,5
	2012	2606	24,72	n.d.		1,2	1,7	65	35	956	5,71	n.d.		2	3,2	56,4	43,6
	2013	2410	22,98	n.d.		0,9	1,2	64,2	35,8	845	5,04	n.d.		1,1	2,8	60,4	39,6
	2014	2278	21,85	n.d.		0,7	1,1	63,5	36,5	814	4,84	n.d.		1,6	4,3	61,5	38,5
	2015	2124	20,47	n.d.		0,6	1	67,1	32,9	867	5,13	n.d.		1	3,8	59,6	40,4

n.d.: not defined.

3.5. Discussion

In Portugal, vaccine coverage is above WHO recommendations of 95% vaccine coverage for infectious disease elimination and control, for age cohorts of newborns (2 years old), the national immunization program participation ranges from 96,1% to 99,1% vaccine coverage. Vaccination coverage for the completed schedule for DTPa is as high as 96,1%, for MMR 97,9%, for Hib 98,7%, for MenC 97,3% and for HBV 98,3%. BCG vaccine coverage ranges from 99,1% to 97,5%. Since July 2016 this vaccine is no longer universally recommended, it is now recommended to risk groups (85). According to WHO, BCG vaccine does not prevent primary infection and, more importantly, does not prevent reactivation of latent pulmonary infection, the principal source of bacillary spread in the community, so its impact on transmission of *Mycobacterium tuberculosis* is therefore limited (86). This may explain the high numbers of cases of tuberculosis in Portugal (867 reported cases in 2015) and in the Netherlands (2124 reported cases in 2015) over the studied years, despite high vaccine coverage levels.

Although we did not include Inactivated Polio Vaccine (IPV) in this study, data on the evaluation of NIP 2016, shows that for 2015 age cohort IPV vaccine coverage was 98% (87).

The Netherlands has a centralized (public) vaccination system, as it happens in Portugal, and vaccination is free of charge. In this study, The Netherlands vaccination coverage is considered high but, in some cohorts, it still does not match the 95% recommended vaccine coverage. Other studies conducted in countries with decentralized (private) vaccination system such as Germany, has demonstrated moderate vaccination coverage levels with most traditional vaccinations at 73-80% (88), another study conducted in France demonstrates 83% DTPa vaccination coverage and 83% MMR vaccination coverage (89). These data suggest that public vaccination systems, free of charge, could have an impact on vaccination.

In The Netherlands, HBV vaccine coverage suffered a huge increase over the studied cohorts, it is important to note that it was just in 2011 that HBV was introduced into the NIP (38), this explains HBV 19,7% vaccine coverage in 2010 cohort. In Portugal, this vaccine was introduced into the NIP in 1993 (90). With the introduction of this vaccine in The Netherlands, it is possible to observe a declining trend in hepatitis B reported number cases over the years, with 196 cases in 2010 to 142 cases in 2014. In Portugal, hepatitis B reported number cases are maintaining low levels, with the maximum of 19 reported number cases in 2014.

In this study it is possible to observe vaccination coverage decline over the selected cohorts in the Netherlands, this data is in accordance with other studies published elsewhere (91). The cause of such decline is unknown but it has been reported to the public health institute to be investigated. If this trend continues, the risk of future outbreak of measles increases. As it is recorded in this study, in 2013 a large measles epidemic of 2640 reported

cases took place in The Netherlands, one person died and there were cases with severe illness (92). The vast majority of reported cases were among unvaccinated orthodox Protestant individuals (92). In Portugal, from 2014 to 2016 no cases of measles were reported. So, in 2015 WHO declared that measles and rubella were eliminated in Portugal. Although in our study, from 2010 to 2016, 24 cases of rubella were reported, just 2 cases (1 case in 2014 and 1 case in 2015) were confirmed as lab-positive cases of rubella (93–98). In 2017, 28 laboratory-confirmed measles cases were identified in Portugal, of which 16 were unvaccinated and one unvaccinated teenager died (99). Measles outbreaks have been reported in Europe, such as in Germany, Italy, Spain (100). Mumps prevention benefits indirectly from the efforts made to reach the goal of eliminating measles and rubella in Europe (101). Although the number of cases is still far from disease elimination. In Portugal, reported cases vary from 160 (2012) to 82 (2014), and in the Netherlands, it ranges from 642 (2011) to 38 (2014). A decreasing trend is observed over the years. Studies have shown that the effectiveness of mumps vaccination depends on the time between the first and second dose given (102).

In Portugal, no case of diphtheria was reported since 2010, in the Netherlands just 2 cases of diphtheria were reported, one in 2012 and the other in 2014. Diphtheria case detection is strongly influenced by the availability of laboratory resources, clinical expertise and surveillance systems (103). And the availability of such resources seems to be unevenly distributed in Europe, and very few countries perform toxigenicity testing (103). On May 2015, Spain reported a case of toxigenic diphtheria (104). The case was a 6-year-old voluntarily unvaccinated boy, who died from the disease in a Barcelona hospital (104). This was the first case of diphtheria reported in Spain since 1986 (104).

Cases of invasive H. *influenzae* disease serotype B are rare in Europe, and it has been reported that the disease is most common in the north of Europe (105). In Portugal, the number of cases is very low, from 6 cases in 2014 to 2 cases in 2015. In The Netherlands, the number of cases varies from 37 in 2010, to 22 in 2011. The sustained low number of serotype B cases reported highlights the success of immunization (105).

The number of reported cases of tetanus in Portugal and in The Netherlands, are very low and shows a decreasing trend. Notification rate for tetanus is also very low in the other EU/EEA countries (106). According to ECDC, despite the small number of cases, tetanus is associated with high mortality, which could be prevented by vaccination (106).

Invasive meningococcal disease serotype C cases are low in Portugal as in The Netherlands. According to ECDC, in Europe, serogroup C continues to show a decreasing trend and is proportionally twice as prominent in countries that do not include MenC vaccination in their routine NIP (107). Serogroup B is responsible for the majority of cases of invasive meningococcal disease, predominantly affecting the younger age groups (107). In Europe, a vaccine against serotype B was licensed in 2013 and was estimated to provide protection

against between 73% and 87% of circulating serogroup B strain (107). In some European countries, this vaccine was introduced in the NIP, such as in the United Kingdom (107). This vaccine could be an important target to the Portuguese immunization program.

A notable increase of pertussis notification rate was observed in The Netherlands in 2012, according to this study 12853 cases of pertussis were reported, it represented the highest number of cases reported in EU/ EEA, followed by the United Kingdom (11993 reported cases) (108). In Portugal, 237 cases were reported in 2012, this still represents an increase from 2011 (32 reported cases). These data highlights that vaccine preventable infectious diseases are still a reason of concern, and it is important to maintain the high levels of vaccine coverage to eliminate and control infectious diseases.

3.5.1. Limitations

As a limitation of this study, we did not analyse vaccination coverage per dose. Inactivated polio, human papillomavirus and pneumococcal 13-valent vaccines were not studied.

It is important to note, that we analysed the reported number cases of disease, which lack laboratory confirmation. This means, that the presented numbers do not represent the real number of disease cases. The reported number cases among countries are still influenced by several factors, including differences in surveillance systems, historical or current vaccination policies, and vaccination coverage levels.

4. CHAPTER 4 – SYSTEMATIC REVIEW ON THE FACTORS BEHIND VACCINE HESITANCY AMONG PARENTS IN HIGH-INCOME COUNTRIES

4.1. Introduction

Immunisation benefits were so satisfying that today we are facing the consequences of its own success (7). The dramatic reduction of the incidence of these VPD during the last decades, contributed to the public perception that the severity of the disease and susceptibility to it have decreased (62). As parents have become less familiar with these diseases, they have become more concerned about the safety and necessity of vaccines (7). Perceived risks from VPD have diminished, whereas perceived risks of vaccination have increased and some experts identify the prevalence of concerns, fears and misinformation about vaccines as an indication of declining confidence in vaccines (109,110). It has been reported that in recent years, vaccination has declined in many regions of the world, especially in cases such as the combined Measles, Mumps and Rubella (MMR) vaccination (58).

Strategic Advisory Group of Experts (SAGE) working group defines vaccine hesitancy as a behaviour, influenced by a number of factors including issues of confidence (do not trust vaccine or provider), complacency (do not perceive vaccine's value or need), and convenience (access) (57). Vaccine-hesitant individuals are an heterogeneous group who hold varying degrees of indecision about specific vaccines or vaccination in general (57). They may accept all vaccines but remain concerned about it, some may refuse or delay some vaccines, but accept others; some individuals may refuse all vaccines (57).

Evidence of vaccine-hesitancy trend comes indirectly from several sources, including studies showing that parents are more often requesting vaccine exemptions to school entry requirements and that providers perceive parental vaccine refusal as being more common than in the past (111).

The behaviour of vaccine-hesitant individuals is complex, and determinants of hesitancy are highly variable across time, place and vaccine (112). *H. Larson and Karafillakis* literature review identifies three main cathegories of determinants for vaccine hesitancy; contextual (conspiracy theories, religious fatalism), individual and group influences (vaccine safety, lack of information, low risk/ severity of disease, vaccines not effective, etc) and vaccine and vaccination specific issues (no medical need, access, finantial costs) (113). Vaccine safety was the vaccine hesitancy determinant more frequently recorded in the literature (113).

The WHO SAGE on Immunization has recognized the global importance of vaccine hesitancy as a growing problem (114). Several studies identify vaccine hesitancy factors and

strategies for addressing vaccine hesitancy from a global perpective (57,114,115). Country or region specific studies on vaccine hesitancy are as well available in the literature (116,117).

4.2. Aims

This systematic literature review aims investigate and analyse parents/legal guardians with children aged between birth and 18 years old reasons and beliefs for not vaccinating their child, delaying or doubting of one or more vaccines included in the National Immunization Program (NIP) in high-income countries.

This result can be used to create strategies intended to reduce vaccine hesitancy and consequently, increase vaccine coverage.

4.3. Methods

4.3.1. Eligibility criteria

PICO's methodology was used in this study to define the population, intervention, comparator and outcomes of the study.

4.3.1.1. Type of study

Included studies were observational and qualitative studies respectively cohort studies, cross-sectional studies, focus group, case studies.

Commentary, personal reflection, news, policy and profiles, reports, recommendations, editorials, literature review, cost-effectiveness, economic, effectiveness, efficacy and randomized controlled trial studies were excluded from the systematic review.

4.3.1.2. Population

Parents/Legal guardians with children aged between birth to eighteen years old, living in a high-income country and manifesting immunization doubts, refusal or alternative vaccination schedule other than the recommended one, against one or more vaccines included in the NIP of the living country.

Health professional/health care provider/physician beliefs about immunization were excluded from the study.

4.3.1.3. Intervention

Qualitative intervention study included semi-structured interviews, interviews, focus groups and surveys.

4.3.1.4. Comparator

Parents/ Legal guardians with children aged between birth to eighteen years old, living in a high-income country, which comply with immunization, and vaccinate their children according to NIP.

4.3.1.5. Inclusion and exclusion criteria

Table 7. Inclusion and exclusion criteria of the systematic review.

Inclusion criteria	Exclusion criteria
Parental/ legal guardian, perception/ behaviour towards immunization studies;	Population study is a health care provider/ practitioner/ physician/ health professional;
Publications between 2006 and 2017;	The subject of the intervention is pregnant women;
High-income countries (classification from The World Bank (114));	HPV and seasonal influenza vaccines;
All National Immunization Programs implemented in high-income countries;	Not related to vaccine hesitancy beliefs/ reasons;
All vaccines and vaccine combinations included in the NIP of the studied country/ region.	Study about the disease itself and do not present parent perception toward vaccination;
Language: English and Portuguese;	Catch-up campaign Study;
	New vaccine implemented in NIP;
	Non-human species study;
	Study about vaccine coverage and do not present parent perception toward vaccination;
	Population study is a minority community;
	Children with medical exemption;
	Do not present reasons to justify parental vaccine hesitancy.

4.3.2. Information sources

The systematic literature search was conducted in February 2017, databases included were PubMed, Web of Science and Science Direct. In this search, the limits used were publications from 2006 to 2017, in Portuguese and English languages and in the human species.

4.3.3. Search

Search keywords were predefined (table 6).

Table 8. Keywords applied to the systematic review search.

Vaccin*	AND	Attitude	Choice	AND	Child*	NOT	HIV
Immunis*		Behav*	Hesitanc*		Paediatric		HPV
Immuniz*		Belief	Concern				Pregnan*
		Accept*	Trust				
		Confidence	Perception				
		Doubt	Anti-vaccin*				
		Distrust	Antivaccin*				
		Exemption	Uptake				
			Movement				

Pubmed search: ((((vaccin* OR immunis* OR immuniz*)) AND (attitude OR behav* OR belief OR accept* OR confidence OR doubt OR distrust OR exemption OR choice OR hesitanc* OR concern OR trust OR perception OR anti-vaccin* OR antivaccin* OR uptake OR movement)) AND (child* OR paediatric)) NOT (hiv OR hpv OR influenza OR pregnan*)

4.3.4. Study selection

Results were collected and duplicates were removed. Eligibility criteria were applied to the remaining articles by one reviser. In a stepwise methodology, consisting on tree distinct phases, title screening, abstract screening and full text analysis. EPPI-Reviewer 4 tool was used for that purpose. Studies were eligible for inclusion in the systematic review if they reported parents/ legal guardians of children (≤18 years old), living in a high-income country (according to The World Bank classification (118)), reasons/ motivations/ beliefs for doubting immunization, changing the recommended vaccine schedule or refusing vaccinate their child against one or more vaccine preventable disease included in NIP of their living country.

4.3.5. Data collection process

After study selection, data was collected and analysed using codification and synthesis method for qualitative data.

Information extracted from the studies included details on vaccine hesitancy factors/ beliefs/ motivations, this text was codified in a descriptive way so that we could create final analytical themes. The qualitative software ATLAS.ti version 7.5 (Scientific Software Developments) was used to assist in data analysis.

4.3.6. Risk of bias

The Effective Public Health Practice Project (EPHPP) quality assessment tool was applied to assess and evaluate the risk of bias of each individual study.

4.3.7. Synthesis of results

Statistical analysis was performed with resource to SPSS software (version 24.0). Absolute and relative frequencies of the total number of vaccine hesitancy themes found throughout the selected articles and the relative frequency of articles that exhibit one vaccine hesitancy factor were calculated.

4.4. Results

Keyword based search identified a total of 19308 articles (PubMed – 5041 articles, Web of Science – 3698 articles, Science Direct – 10569 articles). After duplicates removal, 17323 articles were analysed by title and 422 articles by abstract using EPPI-Reviewer 4 tool. 101 articles were included for a full-text review considering inclusion and exclusion criteria. From these articles, 74 studies were excluded based on the exclusion criteria. A total of 27 articles were included for analysis, published between 2006 and 2016 and comprising a total of 54786 participants (range: 20 – 18488) (figure 30).

The characteristics of each study included in the systematic review is set out in table 9.

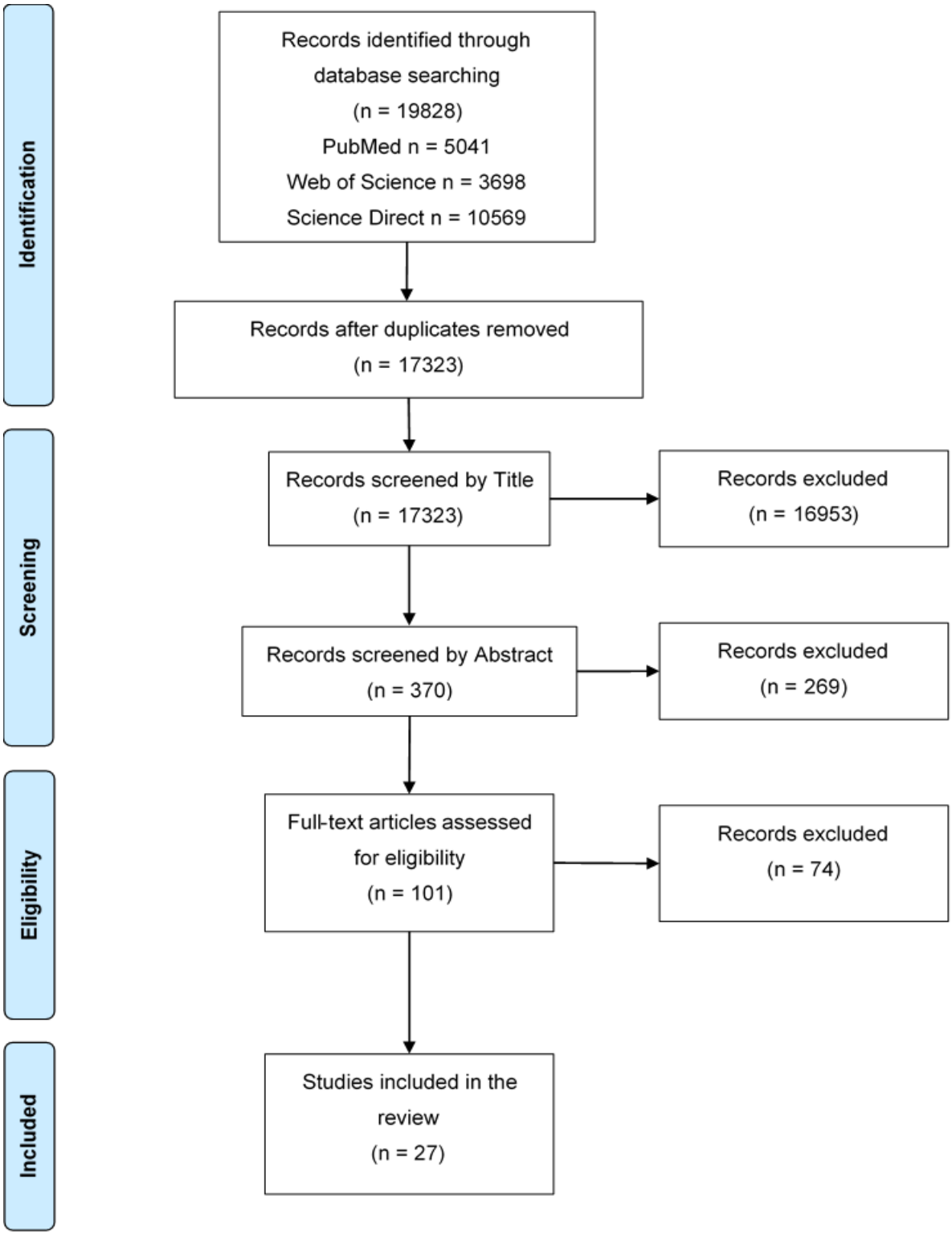

Figure 30. Flow diagram of included studies in the systematic review, adapted from (119).

The majority of articles focused on childhood vaccines in general (n=19) and were not specific to one vaccine, vaccine specific studies were mostly about MMR vaccine (n=6). Other articles focused on HBV vaccine (n=2). Most studies were retrospective, parents were recruited, and their attitudes and beliefs towards immunization were assessed, after they had made their vaccination decision. The vaccine hesitancy beliefs/ factors were typically assessed subjectively with resource to parent-reported intervention or behaviour. Study design included cross-sectional study (n=24), cohort study (one group pre- and post) (n=2) and case-control study (n=1). Out of the 27 articles, the majority were from the United States (n=14), followed by United Kingdom (n=5), Switzerland (n=2), The Netherlands (n=2), Italy (n=2), Spain (n=1) and Canada (n=1).

Vaccine hesitancy factors/ beliefs/ motivations included in each of the 27 selected articles were codified in 20 different themes addressing factors/ reasons/ motivations/ beliefs for parental vaccine hesitancy in high income countries (table 10). For this purpose, one article can refer to more than one theme, we do not take into account the number of times one article records the same theme. Throughout the selected articles we could identify 199 themes, note that although we just selected 20 different themes, the same theme can be found in different articles.

Vaccine safety was the most reported reason of vaccine hesitancy amongst all factors. It was reported in all (n=27) of the included articles. It was followed by low risk perception/ severity of disease (n=19), overloading immune system (n=16), negative exposure to media/ people opinion (n=16), vaccines link to autism/ chronic diseases (n=15), the remaining factors are presented in table 10. The least factors reported by parents for vaccine hesitancy were religious beliefs (n=2), services/ accessibility (n=3) and trauma of immunization process (n=3).

Table 9. Characteristics of studies included in the systematic review.

Author/ year of publication	Country	Aim	Population of interest	Sample size	Data collection period	Study design	Intervention	Vaccination of interest	Risk of bias
A. Smith, Yarwood, and Salisbury 2007	UK	To demonstrate how attitudes in relation to MMR have evolved over the last 10 years incorporating the periods of time before, during and after the height of the MMR controversy within the UK.	Mothers of children aged less than 36 months.	1016	October and November 2006	Cross-sectional study	Interview	MMR	Moderate
Bigham et al. 2006	Canada - British Columbia	To evaluate hepatitis B immunization coverage among the first six-month cohort of eligible infants in the province outside of the Vancouver-Richmond health region and to assess parent/guardian behavioural and attitudinal determinants of HB immunization.	Parents of children (15 months to 2 years)	487	October 2002 and January 2003	Cross-sectional study	Survey	HBV	Moderate
Blaisdell et al. 2016	USA - Maine	To explore perceived and constructed personal judgments about the risks and uncertainties associated with vaccines and vaccine preventable diseases and how these subjective risk judgments influence parents' decisions about childhood vaccination.	Parents of children (0 to 8 years), residing in the greater Portland, Maine, area.	42	not defined	Cross-sectional study	Focus group	Childhood vaccines	Moderate
Borràs et al. 2009	Spain - Catalonia	To investigate parental knowledge of paediatric vaccines and vaccination in Catalonia.	Parents of children born in October 2001 in Catalonia.	630	October 2003 and September 2004	Cross-sectional study	Survey	Childhood vaccines	Moderate
Brown et al. 2011	UK	To develop and validate a scientifically robust and practically feasible MMR attitudes measurement instrument, aiming to overcome methodological limitations currently inhibiting the evidence base through evidence-based item selection, psychometric validation, and objective outcome assessment.	Parents of children (4 to 16 years).	535	May and December 2009	Cross-sectional study	Survey	MMR	Moderate
Brown et al. 2012	UK	To obtain an up-to-date, comprehensive and methodologically robust picture of general factors underlying parents' decision-making about the first dose of MMR.	Parents of children 11 months and 3.5 years.	24	June 2008 and March 2009	Cross-sectional study	Semi-structure interviews	MMR	Moderate
Coniglio et al. 2011	Italy - Sicily	To explore the issues surrounding parental acceptance or non-acceptance of the recommended vaccinations for children.	Parents of children aged 3-5 years of day-care centres in Sicily.	1218	October and December 2008	Cross-sectional study	Survey	Childhood vaccines	Strong
Dempsey et al. 2011	USA	To describe national patterns of alternative vaccination schedule use and the potential "malleability" of parents' current vaccination schedule choices.	Parents, stepparents, or guardians of children 6 months to 6 years of age.	748	May 2010	Cross-sectional study	Survey	Childhood vaccines	Moderate

Fadda et al. 2016	Italy	To gain insights from parents residing in a low measles-mumps-rubella (MMR) uptake area on what constitutes feelings of empowerment in the decision they have to make on their child's MMR vaccination.	Parents with at least one child aged less than 1 year or for whom an MMR vaccination decision was still pending, and be residing in Italy.	28	March and May 2015	Cross-sectional study	Focus group	MMR	Moderate
Freed et al. 2010	USA	To characterize the current prevalence of parental vaccine refusal and specific vaccine safety concerns and to determine whether such concerns were more common in specific population groups.	Parents of children who were aged 17 years.	1552	January 2009	Cross-sectional study	Survey	Childhood vaccines	Moderate
Gross et al. 2015	Switzerland	To understand the influence of parents' emerging views linked to "natural and healthy" lifestyles on their decision regarding childhood vaccination.	Parents of children (0-16) who had either been immunized incompletely, partially or who had not been immunized at all.	32	2011	Cross-sectional study	Semi-structure interviews	Childhood vaccines	Moderate
Harmsen et al. 2013	The Netherlands	To attain more insight into the factors behind immunization decisions among Dutch parents.	Parents with children (0–4 years old).	60	November and December 2011.	Cross-sectional study	Focus group	Childhood vaccines	Moderate
Hontelez et al. 2010	The Netherlands	To identify the determinants of HBV vaccine acceptance and explain the large difference between DPT-IPV-Hib and HBV vaccine coverage among the population eligible for HBV vaccination in the NIP. To determine the attitude towards universal HBV vaccination among parents of HBV eligible and non-HBV-eligible children.	Parents of children born in 2003–2005 and registered in the national vaccination registration database 'Praeventis'.	198	not defined	Cross-sectional study	Survey	HBV	Moderate
Kennedy et al. 2011	USA	To examine the notions of confidence in vaccines and hesitancy about their use, building on recent efforts to understand parents' beliefs and behaviours related to routinely recommended childhood immunizations.	Parent or guardian of one or more children age six or younger.	376	2010	Cross-sectional study	Survey	Childhood vaccines	Moderate
Kennedy, Basket, and Sheedy 2011	USA	To describe the vaccine-related attitudes, concerns, and information sources of US parents of young children.	Parents with at least 1 child aged 6 years or younger.	475	August and september 2009	Cross-sectional study	Survey	Childhood vaccines	Moderate
Lieu et al. 2017	USA	To describe parents' (1) perspectives on how to improve the process, (2) rationales for use of nonstandard vaccination approaches, and (3) reactions to hypothetical alternatives to the standard schedule.	Parents of children (0 to 5 years).	1222	not defined	Cross-sectional study	Survey	Childhood vaccines	Moderate
Luthy et al. 2012	USA - Utah	To explore personal beliefs of parents living in Utah, who exempted their children from receiving vaccinations.	Utah parents seeking to exempt a child from vaccinations for personal reasons.	287	August 2007 and May 2008	Cross-sectional study	Survey	Childhood vaccines	Moderate
Luthy, Beckstrand, and Callister 2010	USA - Utah	To determine why parents in a Utah community hesitated in immunizing their children.	Parents of under-immunized children in the county health department and local paediatric and family practice offices.	86	not defined	Cross-sectional study	Survey	Childhood vaccines	Moderate

Niederhauser and Markowitz 2007	USA - Hawaii	To explore the barriers to immunizations in parents whose children are not fully immunized by age 2.	Parents of 2- to 4-year old children who were not fully immunized at age 24 months.	64	December 2003 and july 2004	Cross-sectional study	Focus group	Childhood vaccines	Moderate
P. J. Smith et al. 2011	USA	To evaluate the association between parents' beliefs about vaccines, their decision to delay or refuse vaccines for their children, and vaccination coverage of children at aged 24 months.	Households that have children aged 19–35 months.	11206	2009	Cross-sectional study	Survey	Childhood vaccines	Moderate
Pearce et al. 2008	UK	To estimate uptake of the combined measles, mumps, and rubella vaccine (MMR) and single antigen vaccines and explore factors associated with uptake and reasons for not using MMR.	Parents of children born in the UK, 2000 – 2002.	14578	not defined	Cohort study (one group pre- and post)	Interview	MMR	Moderate
Salmon et al. 2009	USA - Wisconsin	To determine differences in vaccine attitudes, beliefs, and information sources among parents of children with nonmedical exemptions to ≥1 vaccines compared with parents of fully-vaccinated children in Wisconsin.	Parents of children with nonmedical exemptions (cases) and parents of fully-vaccinated children (controls).	963	not defined	Case-control study	Survey	Childhood vaccines	Moderate
Samad et al. 2006	UK	To analyse the reasons given by mothers for partial and no immunisation in infancy in a nationally representative study.	Parents of children born in the UK, 2000 - 2003	18488	not defined	Cohort study (one group pre- and post)	Interview	Childhood vaccines	Moderate
Senier 2008	USA	To understand parents' beliefs on risk perception and trust in the context of parental decision making about vaccines.	Parents of children (18 months to 16 years).	20	August and November of 2004.	Cross-sectional study	Semi-structure interviews	Childhood vaccines	Moderate
Wang, Baras, and Buttenheim 2015	USA - Philadelphia	To understand how parents, make vaccination decisions, how their vaccine concerns translate into deviations from the recommended schedule despite general acceptance of vaccines, and how they view others' decisions not to vaccinate.	Parents of children (18 months to 6 years) in an upper-middle class neighbourhood in Philadelphia.	25	July and September 2010	Cross-sectional study	Semi-structure interviews	Childhood vaccines	Moderate
Weiss, Schröpfer, and Merten 2016	Switzerland - Aargau	To identify distinct patterns of attitudes towards or against measles vaccination through Latent Class Analysis (LCA) in a sub-sample of mothers living in the canton of Aargau in Switzerland.	Parents of young children below 36 months of age.	189	2011	Cross-sectional study	Survey	MMR	Moderate
Wheeler and Buttenheim 2013	USA	To examine factors associated with a parent's intended choice of vaccine schedule using medical record data routinely collected during a well-baby visit at a private paediatric practice.	Parents of infant less than one year of age at the time of vaccine counselling.	237	December 2009 and April 2011	Cross-sectional study	Medical record data assessment	Childhood vaccines	Moderate

Table 10. Analysed theme factors behind vaccine hesitancy in the systematic review.

Factors behind vaccine hesitancy	Absolute frequency (N)	Relative frequency (%)	References
Vaccine safety	27	13,57%	(53,56,62,64,110,120–141)
Low risk perception/ severity of disease	19	9,55%	(53,64,110,120–122,124–126,128,131,132,134–139,141)
Negative exposure to media/ people opinion	16	8,04%	(53,62,64,121,122,124,127,129–132,135–137,140,141)
Overloading immune System	16	8,04%	(64,110,120–122,127,128,130,131,134–139,141)
Vaccines link to autism/ chronic diseases	15	7,54%	(62,64,110,121,124,127–132,135,136,139,140)
Immunization perceived as negative on the immune system	13	6,53%	(64,120,122,125,126,128,129,131,135–137,139,141)
Vaccine ingredients	11	5,53%	(64,110,121,128,130,131,134,136,137,139,141)
Alternative prevention methods	10	5,03%	(64,120,123,124,127,129,131,135–137)
Previous negative experiences	10	5,03%	(64,120,122–124,128,132,135,136,141)
Vaccine effectiveness/ utility	10	5,03%	(56,64,120,127,130–132,134–136)
Lack of appropriate research	8	4,02%	(64,110,120,122,132,136,139,141)
Mistrust in government and pharmaceutical companies	8	4,02%	(124,126,129,131,136,137,139,141)
Mistrust in health professionals	7	3,52%	(121,124,129,131,136,137,140)
Disease are beneficial	6	3,02%	(64,120,122,124,131,136)
Medical reasons	6	3,02%	(62,64,121,123,127,141)
Parental issues	5	2,51%	(122,123,127,135,141)
Parental knowledge	4	2,01%	(129,138,140,141)
Services/ accessibility	3	1,51%	(123,135,141)
Trauma of immunization process	3	1,51%	(138,139,141)
Religious beliefs	2	1,01%	(125,141)
Total	199[a]	100,00%	(53,56,62,64,110,120–141)

[a] Interventions could address more than one determinant of vaccine hesitancy.

4.4.1. Vaccine safety

All studies included in the systematic review cited vaccine safety as one of the factors leading to vaccine hesitancy, it represents 13,57% of all recorded themes. Parental concerns about the safety of vaccination includes, vaccines perceived as an unnatural substance responsible for weakening the organism, causing mild to serious side effects/ adverse events, including serious diseases and long-term side effects. Safety concerns may be associated just to some vaccines or to vaccines in general.

4.4.2. Low risk perception/ severity of disease

According to this study, low risk perception is the second most recorded theme (9,55%). Most parents perceive vaccine preventable diseases as mild illnesses, not severe if contracted and easily treated. Most believe that the experience of contracting the illness and its recovery is associated with progress in the child's development, so that some parents prefer natural immunity over vaccination. Vaccine hesitant parents consider VPD rare in their living high-income country, they believe their children are not at risk of contracting a communicable disease.

4.4.3. Negative exposure to media/ people opinion

Conflicting risk information and negative stories are presented by various sources as the media, internet web sites and Facebook pages. It may create parental indecisions regarding immunization. People in the social environment, as friends and family, may influence the parental choice to delay or refuse vaccination.

4.4.4. Overloading immune system

One of the most reported parental concerns is administering multiple vaccines at once at a young age (8,04%). Some parents fear that administering combined vaccines could overload or overwhelm the child's immune system.

4.4.5. Vaccines link to autism/ chronic diseases

Some parents believe that vaccination may cause learning disabilities such as autism in healthy children, neurological conditions or brain hyper-inflammatory response. They believe that vaccines may cause chronic diseases as seizures, attention deficit with hyperactivity disorder, diabetes, asthma or immune system problems.

4.4.6. Immunization perceived as negative on the immune system

According to parental opinion, immunization is generally perceived as artificial, unnecessary and it is seen as a negative intrusion into the development of a natural immune system, which may weaken and damage the child's immune system.

4.4.7. Vaccine ingredients

There are parental concerns about unsafe ingredients which some vaccines contain or have contained. Such as thimerosal, aluminium, potential allergens, mercury, heavy metals, adjuvants and preservatives, neurotoxins, formaldehyde and DNA from other animals.

4.4.8. Alternative prevention methods

Many parents argue that the strength of the immune system can be built up by healthy environment, such as good nutrition, raise children in a small-scale home, part-time work, exposure to low-level pathogens, non-smoking environment with access to excellent medical care, isolation from geographic areas of disease and avoidance of traveling. Breastfeeding was mentioned as a sufficient measure to protect infants. Most of parents who held these beliefs showed a particular preference for homeopathy, naturopathy and chiropractors.

4.4.9. Previous negative experiences

Parents' previous experiences of adverse events following immunization that have occur to themselves as a child, or to their own children, are reported as an important barrier to immunization. Parental knowledge on these events, stories of negative experiences towards immunization, or medical problems due to an AEFI, in a family member, friends or other social environment are as well cited in this study.

4.4.10. Vaccine effectiveness/ utility

In parents' opinion, vaccination is seen with a lower quality of acquired immunity compared to the natural means, the uncertainty about the body reactions to it, and it's artificial timing are of a big concern to these parents. Some vaccines are defined by them, as unnecessary and not sufficiently effective.

4.4.11. Lack of appropriate research

Many parents argue that vaccines are administered to the child without really knowing what it triggers. Scientific research is seen as inadequate, they believe that vaccines are not tested enough for safety and that there are no long-term studies of vaccines.

4.4.12. Mistrust in government and pharmaceutical companies

Parental concerns include the belief that childhood vaccination is of financial interest to other parties, particularly pharmaceutical industries and the government. Some parents express scepticism about the role of pharmaceutical companies in drug safety.

4.4.13. Mistrust in health professionals

Some parents concern about the trustworthiness of the border public health network. These parents do not trust clinicians' reassurances about vaccine safety or do not perceive the paediatrician to be competent.

4.4.14. Diseases are beneficial

Childhood diseases are not perceived as a threat but as part of the natural way to strengthen the organism and to acquire natural immunity. Parents associate the experience of illness and recovery to progress in the child's development, they believe that contracting the disease provides superior protection against infectious diseases than immunization.

4.4.15. Medical reasons

Some parents alter vaccine schedule due to the child being sick, unwell, with respiratory infections or in the hospital at the time of the appointment. Medical reasons cited by these parents included chicken pox, salmonella infection, diabetes, eczema, allergy to dairy foods or being premature. Mild conditions such as colds or teething problems were cited as well.

4.4.16. Parental issues

Some parents confess that they are unable to keep appointment due to complex schedules and work, administrative difficulties (costs of transportation, health insurance services), transportation problems, or just because it is complex to get the children to the clinic. Parental substance abuse, neglecting their children, lack of motivation to get the child to the clinic, forgetting the appointment and parental lack of personal organization are among the reasons why parents do not get to the clinic.

4.4.17. Parental knowledge

Some parents expressed doubts about vaccination due to lack of information, personal low perceived competence to decide whether to vaccinate, misunderstanding the importance of immunization, and a small proportion of parents were unaware of NIP.

4.4.18. Services/ accessibility

Parents reported problems with health services and accessibility, such as availability of appointments and vaccines, and no accommodations for lost vaccination records.

4.4.19. Trauma of immunization process

The trauma of the immunization process for both parent and/ or child is among the cited reasons for hesitancy. Some parents confessed their fear over needles and showed their concern over the painful process of administering multiple injections to their children.

4.4.20. Religious beliefs

Religious beliefs were cited as a barrier to immunization.

4.5. Discussion

The qualitative systematic review preformed in this study identified parent's reasons/ motivations/ beliefs for doubting immunization, changing the recommended vaccine schedule or refusing vaccinate their child. The majority of studies were conducted in the United States and in the United Kingdom. Leask et al. identified a spectrum of parental attitudes on immunization and developed five groups of parents. These include unquestioning acceptors, cautious acceptors, hesitant parents, late or selective acceptors, and those who refuse all vaccines (142). A variety of factors were identified as being associated with vaccine hesitancy, each factor is complex and it can vary across time, place and vaccine type (57).

In this study, we can identify parent-specific characteristics, vaccine factors and disease factors that lead to vaccine hesitancy. Vaccine factors include vaccine safety, immunization perceived as negative on the immune system, vaccines link to autism, immune system overload, vaccine ingredients, vaccines effectiveness and utility and lack of appropriate research on vaccine development. Vaccine safety was the most recorded factor of vaccine hesitancy throughout studies, it was recorded in all the 27 studies included in the systematic review. This data is consistent with other studies addressing vaccine hesitancy (113,143). In Larson et al. study, the most common determinant of vaccine hesitancy in Europe was the concern or fear about vaccine safety. Which may include many specific beliefs, but is overall a problem of risk perception (113). Kestenbaum and Feemster study argues that parental immunization decision is influenced by their perceived risk of vaccine preventable diseases. As long as vaccines continue to be successful, the risk of obtaining a vaccine preventable disease may not motivate parents to immunize their children. Instead, parents are more

focused upon vaccine safety and raise concerns about potential short-term and long-term side effects (144).

Disease factors include low risk perception and severity of disease and the belief that diseases are beneficial. Parents who refuse vaccination believe that side effects of vaccines are more severe than the disease itself. They believe that their child is not susceptible to the VPD, so they are more willing to take the risk of being infected by the disease than vaccinating their children due to fear of severe side effects.

Dube et al. study outlines that a wide variety of parent-specific characteristics such as past experiences with health services, family histories, feelings of control, friends influences, can impact the decision-making process regarding vaccination (145).

In this study, parent-specific characteristics include negative exposure to media or to other people opinion, mistrust in health professionals, government and pharmaceutical companies, previous negative experiences, religious beliefs, alternative prevention methods, medical reasons, trauma of immunization process, availability of appointments and vaccines, parental issues and parental knowledge. Negative exposure to media is recorded in 16 out of the 27 studies included in this review. According to Dube et al., the internet has offered an opportunity for anti-vaccination activists diffuse their message, negative stories about vaccine safety in the news and on television correlate with increased incidence of vaccine preventable diseases (145).

4.5.1. Limitations

The systematic review may be subject to several limitations, the study selection and coding was performed by one single author, this may lead to interpretation bias.

The qualitative design nature of the studies included in the systematic review was advantageous in allowing in-depth exploration of participants' perceptions. However, most findings are contingent on retrospective self-report, which can be unreliable and subject to recall and interpretive bias. Thus, it may be subject to social desirability bias, parents may be compelled to give a socially expected answer. The cross-sectional design means that we cannot draw conclusions about causality, it is not known if the subject's attitudes and concerns preceded or followed his behaviour. Most of the studies employed retrospective design in which attitudes were measured after vaccination was received. Participants who agreed to participate were probably more receptive to preventive actions than the general population. Some studies included in this review include potential for non-response bias.

5. CHAPTER 5 – CONCLUSIONS AND FUTURE RESEARCH

Adverse drug reaction reporting to vaccines in the Portuguese paediatric population is slightly decreasing over the years, accounting for 6% of the total ADR received by the National Pharmacovigilance System. The system organ class most frequently involved was general disorders and administration site conditions, followed by injury, poisoning and procedural complications. From the total ADR reports in this study, 55,33% adverse reactions were considered serious, this was a lower value comparing this data to the total number of serious cases of ADR reports concerning all medicines in Portugal during the same period (74.43%).

The ADR underreporting is an important issue, which difficult the real risk/ benefit assessment of any medicine, including vaccines. It is difficult to show in this study the real picture of ADR reporting to vaccines due to the well-known underreporting rate, but we estimate that a significant percentage is missing. It is of the utmost interest in terms of public health to improve the spontaneous ADR reporting, although our national authorities and pharmacovigilance system have hugely improved in the last decades, we have still a considerable work to do. It is necessary to create better measures to improve the voluntary adhesion of health professionals in the assessment of drug safety, and to encourage the patient (or its legal guardian in the vaccine context), to report their adverse events, since these ones will benefit the most of the risk assessment of medicines.

Vaccination coverage in Portugal is very high, and it is increasing over the years. In contrast, in The Netherlands vaccination coverage does not comply with the 95% vaccine coverage recommended by WHO, for all vaccines, and it is been reported that vaccine coverage is decreasing in the past years. The vaccine coverage difference between these two high-income European countries may be a major reason for the diseases outbreaks felt in The Netherlands. Comparing Portuguese vaccine preventable disease cases to The Netherlands cases, we can observe a huge difference. In Portugal, vaccine preventable disease cases in the paediatric population is consistently lower than in The Netherland.

Parental risk perception of adverse drug reactions to vaccines is playing an important role on parental compliance with the national immunization program in high-income countries, which may lead to vaccine hesitancy or vaccine refusal. Although at this moment, in Portugal, we do not have records of vaccine hesitancy it is important to predict such actions.

Vaccination has shown its incredible results in the control of several diseases, our national immunization program distributes the included vaccines for free, it is available to any citizen. It is our responsibility to vaccinate our children in order to maintain high vaccination coverage to avoid disease outbreaks and to protect our population from the well-known effects of this devastating diseases. Although vaccine administration is not mandatory in our country, we

must consider the long-term effects of our decisions, and not only the short or medium-term effects which adverse drug reaction to vaccines represent. It is a civil duty to maintain the success of our national immunization program, and the safety of our population.

For future studies it would be of a major interest to analyse vaccination decision making in the Portuguese population, investigate the proportion of vaccine hesitant parents in the community and their main hesitancy motivations.

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